***United States Court of Appeals***

***for the Second Circuit***

# EXHIBITS

# 76-6135

In The

## United States Court of Appeals

For The Second Circuit

THE NATIONAL NUTRITIONAL FOODS ASSOCIATION and SOLGAR, CO., INC.,

*Plaintiffs-Appellants,*

*vs.*

F. DAVID MATHEWS, Secretary of Health Education and Welfare and ALEXANDER M. SCHMIDT, Commissioner of Food and Drugs,

*Defendants-Appellees.*

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P/S

UNITED STATES COURT OF APPEALS
FILED
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A. DANIEL FUSARO, CLERK
SECOND CIRCUIT

*On Appeal from the United States District Court for the Southern District of New York.*

## EXHIBITS

**Volume II, E351 - End**

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*Fig. 1.* Hand of the patient one week after the eating of the halibut liver.

*Fig. 2.* Foot of the patient, scaling at its maximum, three weeks after the incident.

after 3 weeks (Fig. 2), compared to one week for the hands. The slight desquamation of the rest of the body had entirely disappeared by then.

### *Laboratory findings*

Hemoglobin 18.1 g%, erythrocytes 5.04 mill., W.B.C. 5300/mm³, bands 0, polymorphs 59, lymphocytes 32, monocytes 5, eosinophils 3, basophils 1. Blood sedimentation rate: 1/4. Total protein i.S.: 8.5 g%, alb.: 65.5%. Glob.: Alpha₁ 4%, Alpha₂ 7%, Beta 12%, Gamma 11.5%. Serum phosphorus 4.2 mg%, calcium 10.4 mg%, acid phosphatase 0.1 Bessey u., alkaline phosphatase 3.7 Bessey u., Thymol turbidity 1.8 u., ureum 36 mg%, creatinine 0.7 mg%, SGOT 27 u., SGPT 23 u., total bilirubin 0.5 mg%.

Serum lipids (non-fasting): total lipoid 1283 mg%, phospholipoid 12.9 mg%, cholesterol 379 mg%, esters 73%.

These values show no remarkable deviation from the normal, except a slight increase in the L.D.H., 410 u. (norm. 360 u.), which had returned to normal on February 6 (280 u.). The total lipoid and cholesterol values are elevated even for a non-fasting state. In view of the well-known bleeding tendencies in cases of chronic hypervitaminosis A, coagulation studies were performed; all values were within normal limits: recalcification time 187", prothrombin time 15" (control 15"), fibrinogen content 510 mg%, antithrombine immediate: normal, bleeding time 1'42", thrombocytes 220,000 mm³, hematocrit 51%, color serum normal.

### *Serum vitamin A levels*

The serum vitamin A level on February 7 (10 days after the incident) was 250 i.u./100 ml (norm. 80–120 i.u.), due to an intervening weekend this value was not determined until 2 1/2 days after the sample was taken. It is known (5) that serum vitamin A levels may decrease by 50% on standing for several hours. Technically it was not possible to reduced this interval to less than 24 hours. The second determination on February 13, gave a value of 355 i.u., carotene 50 microgram (normal). It is possible that the first value may have been too low as a result of the delay between the taking of the sample and the determination. On March 20, 51 days after the meal his serum vitamin A level was 310 i.u./100 ml.

*Fig. 3.* Histologic section of the left thenar showing hyperkeratosis, acanthosis and hyperemia of the dermis (× 100).

*Histopathologic findings (Fig. 3)*

The biopsy specimen showed a piece of skin with a very wide horny layer, in which slit formation was noticed. The epidermis was built regularly. There was a very wide stratum granulosum. The rete ridges were wide, the dermal papillae narrow. There was some edema and lymphocytic infiltration round the blood vessels of the dermis.

Conclusion: hyperkeratosis, acanthosis and hyperemia of the dermis. These changes are compatible with the diagnosis of vitamin A intoxication.

*Follow-up data on the other crew members*

The remaining crew members of the "Alida" were examined after their return from another journey to the Lofoten, on February 25, 28 days after the incident. The results are shown in Table I.

On February 25 all patients showed desquamation of hands and feet. None had suffered from dizzyness or blurred vision. Vitamin A levels were elevated in all. The highest level was found in case 1, which is the patient described in full in this paper. The trawler was in port again on March 20, 51 days after the incident, and the crew could be inspected once more. All symptoms had disappeared. An exception was patient number 4, who developed strong desquamation of the horny layer of the soles of the feet in the first week of March, which was still present on March 20. No changes remained elsewhere on the body. Vitamin A levels could be determined again in patients 1, 2, 3, 4, 8 and 9.

Table I

| Serial no. | Age | Halibut liver (g) | I.U. vit. A/100 ml serum 25.2.69 | 20.3.69 | Headache | Nausea | Vomiting | Desquamation face | Desquamation trunk | Desquamation hands | Desquamation feet | Ambulant | To bed | Part. ambulant, part. to bed |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 23 | 300 | 355 | 310 | + + + | + | − | + | + | + + + | + + + | − | + | − |
| 2 | 30 | 250 | 250 | 225 | + + | + | − | + | − | − | − | − | − | + |
| 3 | 54 | 150 | 225 | 225 | + + | − | − | + | − | − | − | + | − | − |
| 4 | 32 | 50 | 255 | 350 | + + | − | − | + | − | + + | + + + | − | − | + |
| 5 | 28 | 20 | 250 | | + | + | − | + | − | − | − | + | − | − |
| 6 | 61 | 90 | 190 | | + | + | − | + | − | − | − | + | − | − |
| 7 | 20 | 300 | 175 | | + + + | + + | + + | + | + | + | + | − | + | − |
| 8 | 25 | 200 | 155 | 135 | + + | + | + | + | + | + | + | − | − | − |
| 9 | 31 | 50 | 120 | 155 | + | − | − | − | − | − | − | + | − | − |
| 10 | 46 | 150 | 195 | | + + | + + | + + | + | + | + | + | − | + | − |
| 11 | 45 | 20 | 180 | | + | − | − | − | − | − | − | + | − | − |

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## COMMENT

In the English translation of the diary of Gerrit de Veer (20), which describes the winter of 1596/1597 spent on the island of Nova Zemlya by a group of Dutch sailors led by Willem Barentsz and J. van Heemskerk, who were in search of the Northeast passage to India, the following passage is found on May 31, 1597. It concerns the shooting of a polar bear: "but her death did us more hurt than her life, for after we ript her belly, we drest her liver and eate it, which in the taste liked us well, but it made us all sicke, specially three that were exceeding sicke, and we verily thought that we should have lost them, for all their skins came of, from the foote to the head, but yet they recovered againe, for which we gave God heartis thankes". In the following centuries many whalers and arctic travelers became unpleasantly acquainted with the poisonous qualities of the livers of polar bear (3, 7, 8, 12, 19), and less frequently of eskimo husky (12, 18), bearded seal and greenland fox (18). Several cases of poisoning by fishliver have been recorded. Poslavski (15) described 9 patients who became ill after eating whale liver. Lonie (10) reported intoxication symptoms in a family after the ingestion of shark liver. Similar symptoms have been recorded after the eating of liver of "hapuka" (groper), kingfish, swordfish (8), ishinagi [stereolepis ishinagi (1)], Spanish mackerel (13), and red steenbras (16).

The symptoms of vitamin A intoxication were divided by Knudson (9), into those of acute and chronic intoxications, each occurring in children and adults. We shall limit ourselves to the acute intoxications in adults.

The following symptoms have been described regularly (3, 9, 10, 12, 15). Two to eight hours after the meal a very severe headache occurs, which is usually localized frontally, followed by nausea, vomiting, dizzyness, irritability tachycardia, a feeling of tiredness and an excessive urge to sleep (sometimes for 24 hours!). In the more severe cases there is redness of the face and sometimes of the mucous membranes. Usually there is localized or generalized pruritus. This is followed after 24–36 hours by peeling of the skin beginning around the mouth and spreading over the entire body. The skin of hands and feet sometimes comes off as a whole. Subconjunctival hemorrhages and gingivitis may occur. Usually the symptoms wear off in a few days, sometimes recovery takes longer. The desquamation lasts for several weeks. The symptoms in our patients are quite similar to those described in the literature of patients suffering from acute vitamin A intoxication after eating liver of polar bears, eskimo huskies, certain fish and after the ingestion of high dosages of vitamin A preparations (6). The patient reported in this paper had eaten halibut liver at other occasions without becoming ill. Fridtjof Nansen (14) reports eating polar bear liver in small amounts without ill effect. These observations may be explained by one of the following findings:

1. The concentration of vitamin A in halibut liver oil increases with the size of the liver and therefore with the size of the animal (11). In contrast to mammals, fish may continue to grow after reaching full maturity. As a result some fish in certain species may reach a very large size and weight. With increasing age the accumulation of vitamin A in the liver continues, since only small amounts of this vitamin are required.

2. There is a marked seasonal fluctuation in the vitamin A content of halibut liver mils. It may vary from 8000 i.u./g i February to 106,000 i.u./g in May (11). There is also a seasonal fluctuation in the amount of oil present in the liver. In general there seems to be an inverse relationship between the amount of oil in the liver and the vitamin concentration in the oil.

3. The part of the liver which is eaten may also play a role. The top of the liver lobe of the halibut contains the largest amount of vitamin A (2).

4. Finally the amount of liver eaten may have influence on the symptoms. It can be seen from Table I, that even small amounts of liver eaten have caused symptoms. If we take 100,000 i.u./g vitamin A as probable concentration (11) for this very large halibut liver, the ingestion of 20 g would be equivalent to a dose of 2 million units. Gerber considers this a sufficiently high dose to cause acute symptoms (4). Poslavski's patients developed symptoms exactly similar to those of our patients on dosages of 1–5 million units. It can be seen from Table I, that there is no relationship between the amount of liver eaten, the seriousness of the symptoms, and the serum vitamin A level, which is also in agreement with findings in the literature (6).

## ACKNOWLEDGEMENTS

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# Hepatic Injury in Chronic Hypervitaminosis A

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A 6-year-old girl who suffered from chronic hypervitaminosis A developed hepatosplenomegaly, hepatic dysfunction, and hypersplenism. A liver biopsy specimen displayed large lipid laden Kupffer's cells which were shown to contain vitamin A by fluorescence microscopy. Electron microscopically hepatic injury was indicated by increased lysosomes, focal cytoplasmic degradation, and numerous "light" and "dark" cells. These nonspecific indications of liver cell damage may reflect intracellular release of the biologically active alcohol of vitamin A.

The association of hepatosplenomegaly and chronic hypervitaminosis A has been recognized since the description of Josephs[1] in 1944. However, few clinicopathological correlations have been reported. In this communication we describe the hepatic changes observed by light, fluorescence, and electron microscopy in a 6-year-old girl with hepatic dysfunction and hepatosplenomegaly resulting from chronic excess ingestion of vitamin A.

## Report of a Case

The patient was a 6-year-old white girl who was admitted with a diagnosis of "probable encephalopathy and intracranial hypertension." During the preceding ten days she had suffered from a febrile illness associated with a discharge from the right ear. The night before admission to North Shore Hospital she suddenly became limp and unresponsive. She was admitted to a local hospital where an intravenous infusion of glucose water was started. This was still running when she arrived at North Shore Hospital. The temperature, at that time, was 101 F (38.3 C); pulse rate, 72 beats per minute; respirations, 26 breaths per minute; blood pressure, 120/70 mm Hg; weight, 15.1 kg (33 lb); and circumference of the head, 50 cm. She was a pale, apathetic girl with dry skin, sparse scalp and eyebrow hair, marked cheilosis, and cracked and bleeding lips. The right eardrum was obscured by a seropurulent discharge. A firm spleen was felt 3 cm below the left costal margin. The liver edge was 1 cm below the right costal margin. There was shotty generalized lymphadenopathy. Percussion of the head elicited a "cracked pot" sound. The sclerae were icteric and the optic nerve heads were blurred. The neck was supple. The hemoglobin level was 9.3 gm/100 ml; hematocrit reading, 28%; white blood cell count (WBC), 17,600/cu mm with

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70% neutrophils, 2% stab forms, and 28% lymphocytes. The urine had a specific gravity of 1.022, 3+ acetone, and 8 to 10 WBC per high power field. Sedimentation rate was 38 mm/hr. Total serum bilirubin level was 6.6 mg/100 ml (2.6 mg/100 ml indirect reacting). The other significant blood chemical findings were as follows: blood urea nitrogen (BUN), 10.6 mg/100 cc; carbon dioxide, 15 mEq/liter; sodium, 122 mEq/liter; potassium, 1.8 mEq/liter; and chloride, 122 mEq/liter.

Because of the hypokalemia and hyponatremia, she was given appropriate electrolyte containing fluids intravenously. Because of a reported penicillin sensitivity and the suspected ear infection, antibiotic treatment was started with erythromycin and oxytetracycline (Terramycin) and continued for four days. The morning after admission, she was much more alert. The blurring of the optic discs disappeared by the fourth hospital day. The serum bilirubin level slowly fell during the next few weeks. However, throughout her 4½ weeks in the hospital, the thymol turbidity remained between 6 and 10 units, and the activity of serum glutamic oxaloacetic transaminase (SGOT) stayed between 120 and 160 units. Approximately four weeks after admission, a percutaneous liver biopsy was performed.

The anemia noted on admission became more apparent as hydration improved, the hemoglobin level dropping to 6.3 gm/100 ml. The red blood cells (RBC) were normochromic. The platelet count was 24,000/cu mm. On the morning of the fourth day, she had a severe nose bleed which required cauterization. She then received the first of three transfusions—a total of 750 ml of whole blood was given. On the sixth day, the hemoglobin level was 10.5 gm/100 ml, and the hematocrit reading was 31%. The platelet count was 110,000/cu mm by the eighth day.

Shortly after admission additional significant history was obtained. Because the mother had been told that vitamins were good for the baby, the patient had received varying amounts of cod liver oil or vitamin drops with every feeding ever since she was 18 months old. A pint bottle of cod liver oil (approximately 400,000 units of vitamin A) or 1½ bottles of multivitamin drops (approximately 625,000 units of vitamin A) was consumed weekly. The diagnosis of hypervitaminosis A was confirmed nine days after admission when the blood level of free vitamin A was reported as 825μg/100 cc (normal 6 to 60μg). Radiographs of the long bones showed only moderate demineralization, metaphyseal irregularities, and widening of epiphyseal lines. No cortical hyperostoses were seen. There was no evidence of hypervitaminosis D.

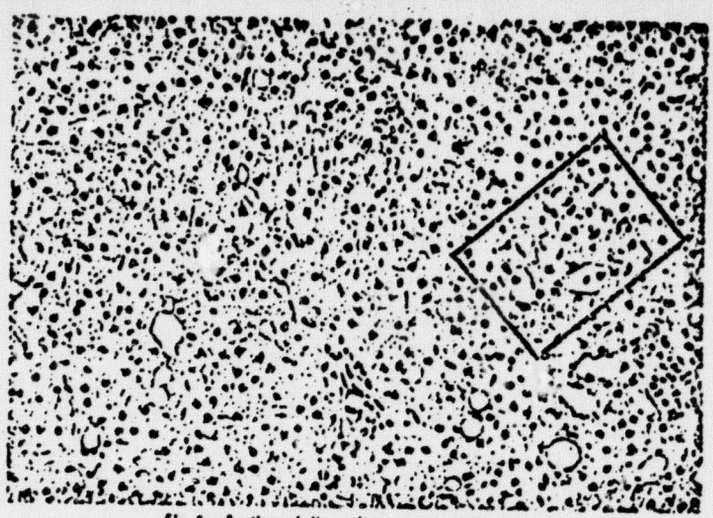
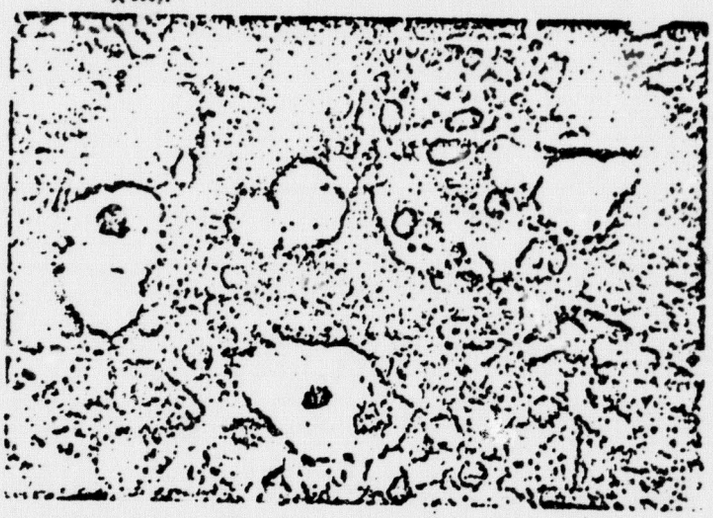


*Fig 1.—Section of liver shows numerous large, pale vacuolated sinusoidal cells (hematoxylin and eosin, × 150).*

*Fig 2.—Higher power of previous figure (boxed area) showing enlarged vacuolated sinusoidal cells (hematoxylin and eosin, × 600).*



When discharged one month after admission, she weighed only 15 kg (33 lb), but she was afebrile, alert, and active. Her appetite had improved. Although her hair was still sparse, the cheilosis and cracked lips were no longer prominent. However, a firm spleen was still felt 3 cm below the costal margin and the liver edge was still 1 cm below the costal margin.

One year later, she weighed 18.1 kg (40 lb), and had a good growth of scalp hair and eye lashes. The liver edge was no longer palpable, but the spleen was still firm and easily felt 3 cm below the costal margin. The hemoglobin



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Fig 3.—Fluorescence micrograph of liver. Sinusoidal cells display intense cytoplasmic fluorescence. Hepatocytes (arrows) display faint fluorescence (× 450).

Fig 4.—Sinusoidal cell showing cytoplasm occupied by large lipid globule which displaces the nucleus (N) (× 14,400).

level was 9.9 gm/100 ml; hematocrit reading, 28%; RBC, 3,200,000/cu mm; reticulocyte count, 3.7%; platelet count, 313,000/cu mm; and WBC, 5,000/cu mm. Hypersplenism was thought to be the cause of the persistent anemia.

### Morphologic Studies

The specimen of liver obtained by percutaneous aspiration with a Menghini needle was divided into three pieces. A portion of the specimen was fixed in 10% solution of neutral buffered formaldehyde solution, and from it paraffin sections were prepared for light microscopy. For electron microscopy, a small fragment was fixed in ice cold 1% osmic acid in veronal acetate, buffered at pH 7.4. After dehydration in graded alcohols, the tissue was embedded in epoxy resin (Epon 812) and thin sections cut on a microtome (Porter Blum). Sections were stained with lead hydroxide and examined with an electron microscope (Hitachi HS-7) in the Pathology Department at the Mount Sinai School of Medicine. The remaining portion of the specimen was snap frozen in 2-butyl alcohol at —70 C. Cryostat sections were examined under ultraviolet light with a fluorescence microscope. For comparison with spontaneous fluorescence, liver tissue from a patient with a nonhepatic disorder was examined in the same fashion.

### Results

By light microscopy the lobular architecture was intact, with normal portal tracts and central canals (Fig 1). The liver cell plates were regularly arranged and the liver cells appeared normal, except for conspicuously increased lipofuscin pigment. Within the sinusoids there were numerous swollen littoral cells. Many of these had a foamy reticulated cytoplasm, while others had a clear cytoplasm (Fig 1 and 2). Several such cells were also seen in the portal tracts.

With fluorescence microscopy, the

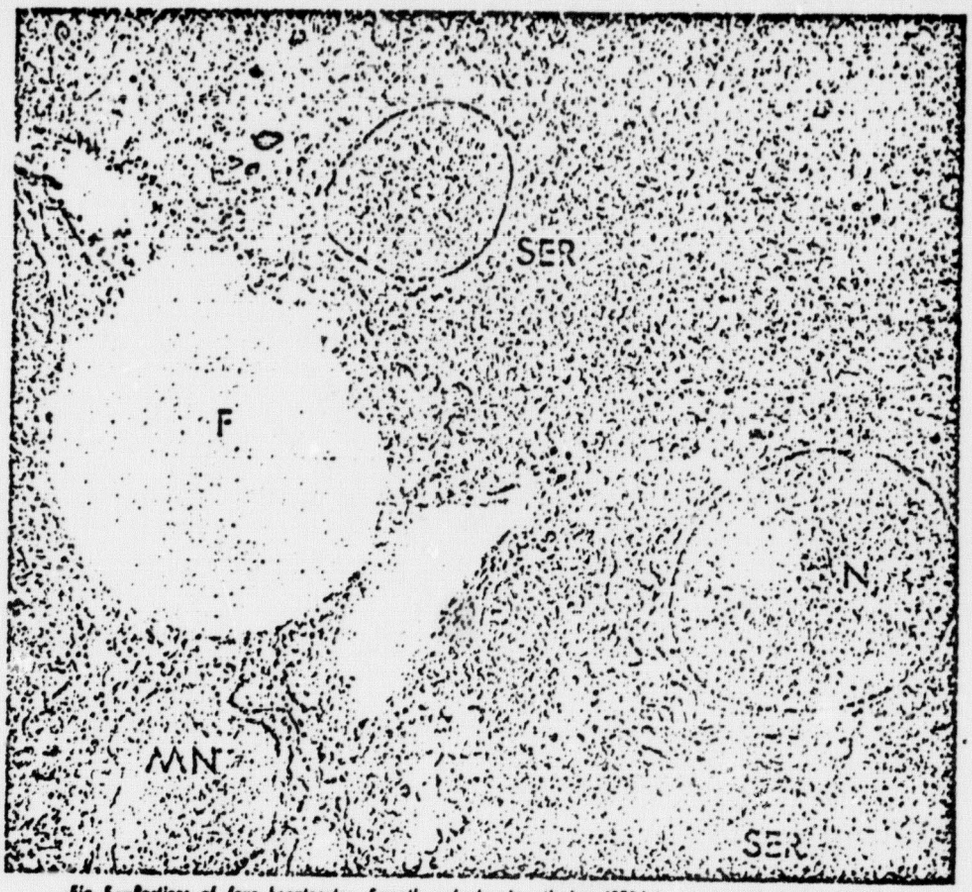



*Fig 5.—Portions of four hepatocytes. Smooth endoplasmic reticulum (SER) is conspicuously hypertrophied. A sinusoidal mesenchymal cell contains a large fat globule (F). MN indicates mesenchymal cell nucleus; N, nucleus (× 6,000).*

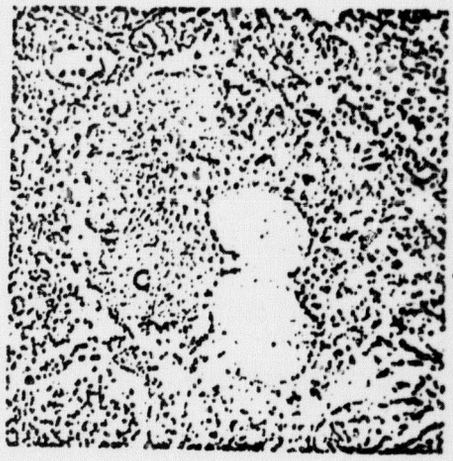
control specimen showed faint fluorescence in Kupffer's cells and occasional fluorescent granules in hepatocytes. In the biopsy from the patient numerous littoral cells and occasional mesenchymal cells in the portal tracts displayed intense green cytoplasmic fluorescence (Fig 3), which faded rapidly with continued exposure to ultraviolet light. Slight diffuse fluorescence was noted in occasional hepatocytes. Fluorescent granules in hepatocytes were common.

Electron microscopic examination revealed numerous sinusoidal cells containing large fat droplets, which occupied most of the cytoplasm (Figs 4 and 5). Similar cells were seen in the portal tracts. In some portal tracts lipid globules which appeared extracellular were noted (Fig 6).

In the hepatocytes the endoplasmic reticulum, mitochondria, and bile canaliculi appeared normal. With respect to other subcellular organelles, the hepatocytes presented a varied appearance, some being entirely normal, while others displayed one or more of the following abnormalities.

(1) Pigment. Most hepatocytes exhibited a variable number of irregularly shaped, heterogeneous, electron opaque bodies composed of sub-

*Fig 6.—Portal tract contains extracellular lipid. C indicates collagen; H, hepatocyte (× 10,600).*



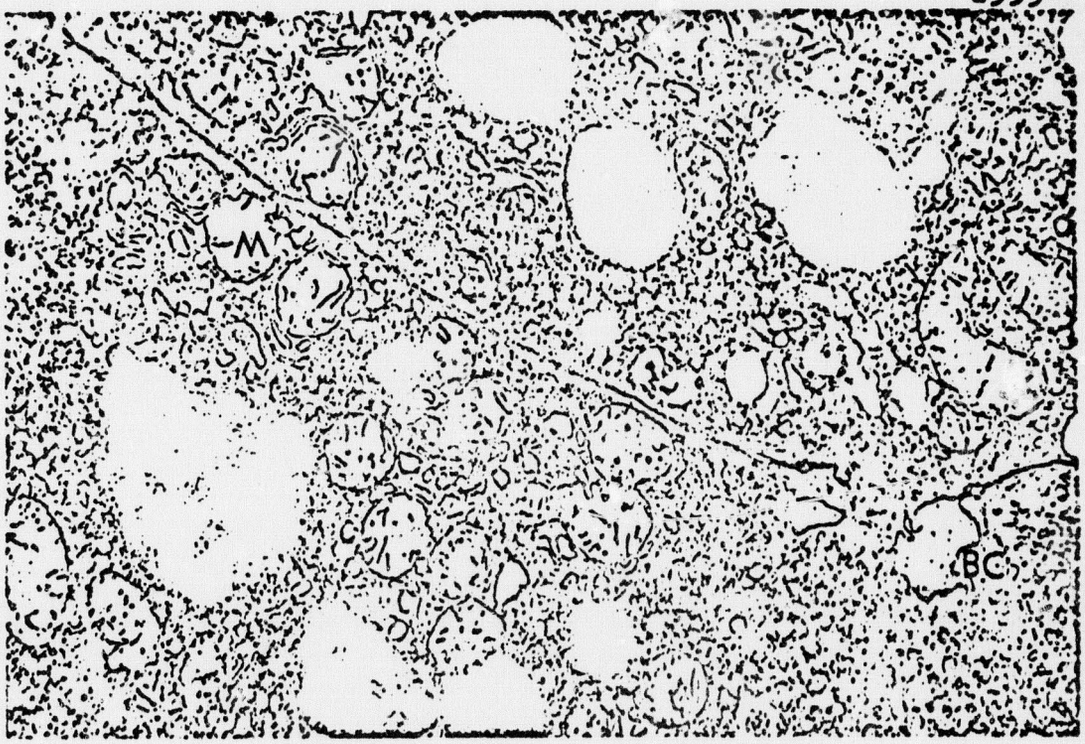



*Fig 7.—Portion of three hepatocytes. Large pigment containing lysosomes are conspicuous. BC indicates bile canaliculus; M, Mitochondrion (× 14,400).*

structures of a variable density (Fig 7 and 8). These were interpreted as lysosomes, were particularly prominent near bile canaliculi, and corresponded to the lipofuscin pigment granules seen by light microscopy.

(2) Focal cytoplasmic degradation was conspicuous, being characterized by numerous small vacuolated foci, which were not delimited by a membrane. Within these residual vacuolated bodies were irregular osmiophilic bodies in the forms of clumps, whorls, and irregular figures, which appeared to be degenerated organelles (Fig 9). Autophagic vacuoles, limited by a single membrane and containing degenerated organelles, were also increased (Fig 8).

(3) Fat. Many hepatocytes contained small lipid droplets (Fig 8).

(4) Smooth endoplasmic reticulum was hypertrophied in a moderate number of hepatocytes (Fig 5).

In addition to these changes, an increased variability in the density of hepatocytes—so-called light and dark cells—was present (Fig 8).

### Hematologic Studies

A variety of tests was carried out to find the cause for the normochromic and normocytic anemia. The bone marrow was highly cellular and contained abundant megakaryocytes, but was otherwise unremarkable. The Coombs' test was negative. Starch block hemoglobin electrophoresis demonstrated 1.8% $A^2$ hemoglobin and 1.5% fetal hemoglobin. The glucose-6-phosphate dehydrogenase activity of the erythrocytes was normal. Three weeks after the last transfusion the patient was injected with her own erythrocytes labeled with radioactive chromium ($^{51}Cr$). The half-life of erythrocytes labeled with $^{51}Cr$ was 17 days (normal 27 to 35 days) and splenic sequestration was demonstrated.

### Comment

The clinical appearance of the patient was similar in most aspects to that described in chronic hypervitaminosis A.[3,4] The mild jaundice, hepatosplenomegaly, and course resembled that of the child described by Josepha.[1] The diagnosis in our patient was established not only by the high blood level of vitamin A, but also by the demonstration of increased vitamin A-like fluorescence in the liver biopsy specimen.[5] In a review of 36 cases of hypervitaminosis A, Oliver [2] pointed out that the signs and symptoms are highly variable, and that individuals and organ

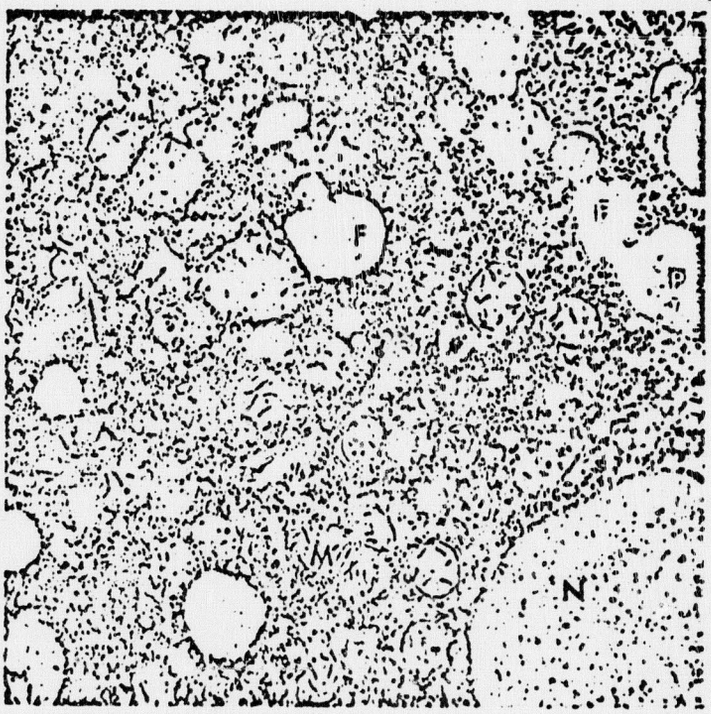



*Fig 8.—Two neighboring hepatocytes, a dark cell on the left and a light one on the right. Both contain fat droplets (F). An autophagic vacuole (arrow) contains a degenerated mitochondrion. P indicates pigment; N, nucleus; M, mitochondrion; G, glycogen (× 10,600).*

systems may vary in their susceptibility to the toxic effects of vitamin A. This may be why the liver and spleen were so prominently involved in our patient.

Hepatosplenomegaly was described in Josephs'[3] original case report and has been observed in subsequent cases of hypervitaminosis A. Nevertheless, we find only two previous reports of liver biopsies.[6,7] Both were in adults, and by light microscopy, were reported as normal, except for lipid droplets in Kupffer's cells in one case.[7] In that case, minimal hepatic dysfunction, characterized by slight prolongation of the prothrombin time and mild elevation of serum alkaline phosphatase activity was noted.

Jaundice, elevated thymol turbidity, and increased activity of SGOT in our patient were clinical evidence of hepatic dysfunction. By light microscopy, the hepatic sinusoids contained large foamy macrophages which displayed the characteristic evanescent fluorescence of vitamin A. Similar fluorescence was also seen within hepatocytes. Hepatic lipofuscin pigment, which is uncommon in children, was prominent in this patient. Electron microscopically, the fluorescent material seen with ultraviolet light corresponded to the large fat droplets in Kupffer's cells, small droplets in hepatocytes, and fat in the portal tracts. Ultrastructural changes in hepatocytes included increased pigment containing lysosomes, lipid droplets, focal cytoplasmic degradation, and increased variability in electron density of

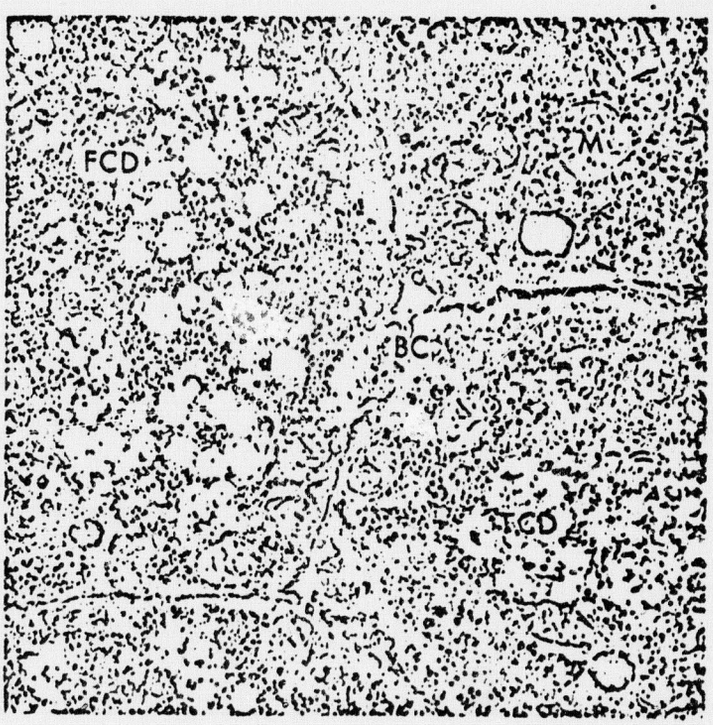



*Fig 9.—Portions of four hepatocytes. Striking focal cytoplasmic degradation (FCD) is noted. G indicates glycogen; BC, bile canaliculus; M, mitochondrion (× 10,600).*

neighboring cells (so-called light and dark cells). These changes probably indicate cell damage, but are nonspecific and may be observed in diverse conditions such as viral hepatitis [8] or alcoholic liver injury.[9] Thus, the hepatic storage of vitamin A in this case was associated with both clinical and structural evidence of liver damage. The hypertrophy of smooth endoplasmic reticulum, which has also been previously noted,[7] is probably a response to increased metabolism of vitamin A, since both synthesis [10] and splitting [11] of the ester are microsomal functions.

The anemia associated with chronic hypervitaminosis A is usually attributed to poor nutrition or blood loss. Although these factors may have played a role in our patient, she still had mild anemia and reticulocytosis one year after stopping the ingestion of excess vitamin A. By that time her appetite had improved and she had gained weight. However, her spleen was still very large. The hypersplenism, demonstrated during her hospital admission by studies with erythrocytes labeled with $^{51}Cr$, probably accounted for her continuing anemia, even though her platelet and leukocyte counts had returned to normal levels.

Vitamin A is transported from the intestine to the liver in the esterified form and stored there as the biologically inactive ester.[12] Hepatic esterases convert it to the biologically active alcohol, which is released into the blood. Excess free vitamin A results in rapid hemolysis of erythrocytes in vitro,[13] alters the appearance and function of embryonic chick cartilage,[14] and induces changes in isolated rat liver mitochondria [15] and lysosomes.[16] The mitochondria swell and the lysosomes release hydrolytic enzymes. These phenomena have been explained by the theory that excess free vitamin A penetrates cellular and intracellular membranes and changes their function.[14] Toxic blood levels of vitamin A in man result not only from excessive intake, but also from an interference with the ability of the liver to control the hydrolysis and release of vitamin A.[12] If excessive amounts of biologically active vitamin were released within a hepatocyte, changes might occur in the lipoprotein membranes of the intracellular organelles. The increase in lysosomes and the focal cytoplasmic degradation seen in our biopsy specimen would be compatible with such an effect.

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Your editorial thus oversimplifies complex phenomena. It implies that all post cardiotomy psychiatric problems are, in effect, merely the product of brain damage produced during the operation. My concern is that the role of a variety of other factors may thus be overlooked and patient care seriously compromised. Earlier reports indicated that patients often experienced a lucid interval of three to four days following surgery and preceding the onset of disorganized mentation.[2-5] This disorder usually cleared within 24 to 48 hours after transfer to a standard hospital environment. These clinical observations suggested that postoperative factors, and specifically the Open-Heart Recovery Room environment, might be playing a role in the production of those symptoms. Subsequently Lazarus and Hagens were able to significantly reduce the incidence of these postoperative psychiatric complications by manipulating a variety of environmental and psychological variables. We agree with Tufo that it is the patient with an organically impaired brain who is most vulnerable to the sleep deprivation and sensory monotony often presented in this environment.

We have observed another smaller group of patients in whom confusion, disorientation, or delirium were apparent on the first postoperative day (D. S. Kornfeld et al, unpublished data).[4,6] These patients were clearly manifesting the effects of organic brain dysfunction produced during surgery. Obviously, in these patients, the postoperative environment could not have contributed to their disorder. It may be that the Tufo series, with its predominantly early onset of symptoms, contains a larger proportion of patients in this latter category.

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*To the Editor.*—Your editorial "Open-Heart Surgery and the Psyche" (212:1370, 1970) is so dogmatic and final! Need there be a "victor?" I think the comments are oversimplistic and show a naivety of the mind-body problem which is frankly rather frightening. If you really read my work, as well as that of others (such as Kornfeld et al),[1] you will find no assertion that all the psychiatric complications following open-heart operations are "functional" in nature. For we are all aware there are a *multiplicity* of factors involved in the patient's response to cardiac operations. Indeed I mention Gilman's article[2] in my original paper,[3] and in other writings note "multiple etiologies" involved in postoperative reactions. At a time when psychiatry is moving toward medicine and psychiatrists are collaborating with their medical and surgical colleagues to understand the *complexity* involved in patients' responses to physical illnesses and operative procedures, let us not attempt to start battles where they do not exist.

Harry K. Abram, MD
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## Need for Controlled Study

*To the Editor.*—The article by Sheldon et al on venous autografts for myocardial revascularization (213: 78, 1970) records a magnificent surgical series from the standpoint of concept and technical ability. Yet the very appealing evidence for success remains inconclusive. Where are the control patients? Surgery is a form of therapy, not a magical process. It must be evaluated like other treatments and by equally high standards, ie, by minimizing bias through random allocation of "qualifying" patients to control and treated groups.

It is equally deplorable that in the same issue (QUESTIONS AND ANSWERS, p 135) Dr. Baue's evaluation of various forms of revascularization is devoid of any reference to the lack of control. My criticism of the surgical enthusiasts is not that they are wrong (or even probably wrong), but rather that they have not attempted to really prove themselves right. Their technical and professional expertise are not in question. The absence of properly designed and controlled studies cuts both ways—the proof remains in limbo.

Again in the same issue (p 131), John Oates rightly deplores the absence of a control series in the report on exercise therapy for hypertension. The points in the reply are well made, but are only tangentially relevant to the real issue.

We would not think of testing a new drug without control patients. Surgical procedures generally are perilous far beyond the side effects of most pills. It is high time that granting authorities, journal reviewers, and therapeutic trials committees demand equal standards of all treatments: appropriately designed and controlled trials.

David H. Spencer, MD
Boston

## Papilledema and Hypervitaminosis A

*To the Editor.*—The letter by Pedontin (212:628, 1970) describing the case of pseudotumor cerebri produced in an 18-year-old girl by hypervitaminosis A, includes the statement, "In none of the cases—adults or children—has papilledema been the only finding." This patient was observed at Ohio State University Hospital.

Oliver and Havener[1] described in 1958 the case of a 14-year-old girl with bilateral papilledema, as well as loss of hair, skin changes, migratory arthritic pains, hepatomegaly and splenomegaly, hypomenorrhea, and generalized malaise. Serum vitamin A levels confirmed the diagnosis of hypervitaminosis A.

Morrice et al[2] in 1960 described three cases in girls 14, 15, and 16 years with diplopia, papilledema, and other symptoms suggesting brain tumor. In addition to various individual complaints, each had hypomenorrhea, alopecia, and rhagades or other marked forms of dermatosis.

Ironically, these four additional cases of papilledema due to hypervitaminosis A were all observed at University and Children's Hospitals associated with Ohio State University.

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pregnancies associated with an I.U.D. A case of ovarian pregnancy associated with an I.U.D. was reported by Piver, Baer and Zachary.[4] This subject has recently been explored by Lehfeldt, Tietze and Gorstein.[5]

Does the presence of an I.U.D. increase the incidence of ectopic pregnancy? Wei,[6] quoting other authors and also from his own experience, believes that it does not, but the question is by no means decided.

I wish to thank Dr. Meredith Silver for examining the surgical specimen.


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## Christmas tree allergy

*To the Editor:*

In their paper "Christmas tree allergy: mould and pollen studies" (*Canad Med Ass J* 103: 1272, 1970) Wyse and Malloch describe 34 patients with skin symptoms and signs which they attribute to Christmas tree allergy. In Table IV they list the following:

| | | |
|---|---|---|
| *Skin:* | Transitory rash..... | 28 patients |
| | Vesicles and exudate | 1 |
| | Angioedema ..... | 3 |
| | Urticaria..... | 2 |

The authors describe the transitory rash as "multiple small, red, itchy or burning spots on the forearms and hands and occasionally on the face, where the skin had contacted the needles; this started within five minutes of trimming or decorating the tree and usually disappeared within half an hour." They suggest that this rash "probably represents a contact allergy to the oleoresin of the balsam".

The morphologic term "spot" does not indicate whether these are macules, papules, patches, plaques, or variants thereof, but the rapid onset of the skin rash does not agree with a diagnosis of contact allergy.

Contact allergic dermatitis is mediated by delayed cellular immune mechanism and does not arise and disappear within minutes. The "transitory rash" which the authors describe is presumably a primary irritant dermatitis due to the contact with the Christmas tree needles or other products of the tree such as bark or resin. Any individual is subject to a similar primary irritant reaction and it does not require stimulation of the allergic process.

Details are not given of the single patient with "vesicles and exudate", but this is a morphologic presentation that may often be seen with contact allergic dermatitis (e.g. as in poison ivy).

True contact allergic dermatitis to numerous products of trees (resins, pollens, sawdust etc.) is well known and well documented in standard texts.[1, 2]

Scratch tests are not accurate in contact allergic/dermatitis and should not supplant the regular patch test.


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## Vitamin A Intoxication

*To the Editor:*

I should like to bring to the attention of the profession the risks of vitamin A intoxication and the ease with which this vitamin can be obtained by over-the-counter sales in this country.

I recently attended a girl aged 15 who developed headaches, vomiting and diplopia, all with acute onset. Strabismus and papilledema were evident on examination and the cerebrospinal fluid pressure was grossly elevated. My original diagnosis was a probable cerebral tumour but extensive neurological investigation was completely negative. The patient had been taking vitamin A in a dosage of 200,000 units daily for two years. She made a complete and dramatic recovery following discontinuation of this medication.

The vitamin had been sold to her over the counter in the drug store in the belief that it would benefit her facial acne. The strength of each tablet was 50,000 units, and while it was recommended on the bottle that only one tablet should be taken each day, the patient was told that it was quite common to take more than this in the treatment of acne. It seems to me that there is a very high risk of inducing "benign intracranial hypertension" in some patients if this vitamin is to be freely available without prescription.


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[Editor's note: A statement by the Canadian Paediatric Society on "The Use and Abuse of Vitamin A" appears on page 521 of this issue.]


*(Continued on page 535)*

Recent reports have brought hospitals for the mentally handicapped under timely scrutiny, but have prompted the point of view that the hospital is an inherently bad institution for the care of the mentally handicapped. This is unfair, because with the exception of a few newly established units most hospitals for the mentally handicapped in this country have not enjoyed the facilities, resources, and staff required to do justice to their patients.

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D. A. SPENCER.

## HYPERVITAMINOSIS A WITH HYPERCALCÆMIA

SIR,—A relationship between vitamin-A intoxication and hypercalcæmia is not generally recognised.[1] Large-dosage vitamin-A capsules may be readily purchased without prescription. We have seen a patient with severe hypercalcæmia associated with hypervitaminosis A. He was taking the vitamin because he had heard that it was beneficial in acne.

A 16-year-old male was transferred from another hospital because of hypercalcæmia of 18·9 mg. per 100 ml., detected by routine admission screening. He admitted to having taken vitamin A for about 6 months, usually 100,000 units a day, but every 4th or 5th day 300,000 units, for treatment of acne. In addition, he was taking vitamin C 500 mg. a day and a multiple-vitamin preparation containing vitamin A 5000 units, vitamin D 400 units, vitamin $B_1$ 2 mg., vitamin $B_2$ 2·5 mg., niacinamide 20 mg., vitamin C 50 mg., vitamin $B_6$ 1 mg., vitamin $B_{12}$ 1 µg., and calcium pantothenate 1 mg. He was also intermittently using an ointment containing vitamins A and D. Several weeks before admission he had developed polyuria and polydipsia, and about five days before admission a sore throat and swollen tender cervical lymph-nodes. The next day he had been feverish (102 °F) and had vomited several times. Two days later he had had general malaise associated with desquamation of the skin about his trunk, upper extremities, and face, along with facial flushing and fissuring of the lips.

On physical examination the patient was dehydrated, confused, and lethargic. The above cutaneous findings were noted. The liver was not palpable. Serum calcium was 18·9 mg. per 100 ml., $CO_2$ 32 m*M* per litre, chloride 98 meq. per litre, potassium 3·2 meq. per litre, alkaline phosphatase 26 units, blood-urea-nitrogen (B.U.N.) 28 mg. per 100 ml., serum-glutamic-oxaloacetic-transaminase (S.G.O.T.) 91 units, and serum-proteins 6·9 g. per 100 ml. (3·2 g. albumin and 3·7 g. globulin). (These determinations were all performed on the 'Auto-Analyzer'.) Repeat calcium determinations before treatment were 18·4 mg. per 100 ml. and 16·7 mg. per 100 ml. The urinary excretion of calcium initially was 1045 mg. per 24 hours. Complete blood-count, serum-protein electrophoresis, and chest X-ray were normal. Urinalysis revealed a trace of protein and 10–15 white blood-cells.

He was started on a sodium-sulphate infusion with added potassium, and surgical exploration was undertaken on the evening of transfer because of the possibility of hyperparathyroid crisis. Four parathyroid glands were found, and all felt normal. One was removed, another biopsied, and a lymph-node was removed. All were histologically normal. He was continued on sodium sulphate and cortisone acetate, 100 mg. every 8 hours, after surgery. On the third hospital day the serum-calcium was 12·5 mg. per 100 ml. and on the fifth day it was 9·7 mg. per 100 ml.; it remained in the normal range when treatment was stopped. The serum-alkaline-phosphatase, urinary calcium, B.U.N., and S.G.O.T. were normal by the eighth hospital day. A prolonged prothrombin-time (35%) was corrected with parenteral vitamin K. Bromsulphthalein excretion was normal. An intravenous pyelogram, bone survey, and bone-marrow examination were normal. The vitamin-A preparation was examined for vitamin-D contamination by gas-liquid chromatography, thin-layer chromatography, and by spectrophotometry. By these sensitive techniques no evidence of contamination was found. The vitamin-A level was 934 I.U. per 100 ml. (normal 65–275 I.U. per 100 ml.), and the serum-carotene level was normal.

An association between experimental and clinical vitamin-A intoxication and increased bone resorption has been reported previously.[2,3] Vitamin-A intoxication associated with hypercalciuria has been described,[4] but only one case has been reported with hypercalcæmia (13·6 mg. per 100 ml.).[5] Our patient had dermatological and hepatic[6] findings of hypervitaminosis A in association with a high circulating level of vitamin A. Thus, the only apparent explanation for the hypercalcæmia was vitamin-A intoxication. We suggest that this should be considered in the differential diagnosis of hypercalcæmia.

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## ACUTE HYPERCALCÆMIC SYNDROME DURING TREATMENT OF OSTEOPOROSIS WITH CALCIUM INFUSION

SIR,—Pak et al.[7,8] put forward the hypothesis that osteoporosis is caused by an imbalance between parathyroid-hormone secretion and calcitonin secretion, resulting in a net loss of bone. To reverse this imbalance they induced intermittent hypercalcæmia in 6 osteoporotic patients by means of 12 infusions of calcium (15 mg. per kg. body-weight per infusion) in 12–21 days. Each infusion lasted 4 hours. Their results were very promising and stimulated interest in this form of treatment.[9]

We have given calcium infusions to 7 patients with osteoporosis (results to be published later). 1 patient, a 70-year-old woman, developed a severe hypercalcæmic syndrome during the 5th infusion. Plasma-calcium was 20·2 mg. per 100 ml. She was treated with phosphate and glucocorticoids intravenously, but her condition improved only after 4–5 days. Before treatment plasma-creatinine was 12 mg. per 100 ml., but $^{51}$Cr-E.D.T.A. clearance showed a glomerular filtration-rate of 36 ml. per 1·75 sq. m. body surface per minute. During the first calcium infusion, plasma-calcium increased from 10·2 mg. per 100 ml. to a maximum of 16·4 mg. per 100 ml., and 20 hours after the infusion it was 13·8 mg. per 100 ml.

On the basis of this experience we suggest that calcium infusions should only be used in treating osteoporosis if (1) the glomerular filtration-rate is normal, and (2) plasma-calcium has returned to normal after the previous infusion.

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# AMERICAN ACADEMY OF PEDIATRICS

## JOINT COMMITTEE STATEMENT
## COMMITTEES ON DRUGS AND ON NUTRITION

# THE USE AND ABUSE OF VITAMIN A

VITAMIN A is an essential nutrient necessary for maintenance of normal epithelial tissue and for optimal growth.[1,2] Impaired dark-adaptation and night blindness are well known manifestations of vitamin A deficiency. Although vitamin A is present in many foods, it cannot be assumed that all individuals receive adequate amounts. Preliminary reports from the recent 10-state nutrition survey* show that a significant proportion of the population has a low intake of vitamin A and low plasma vitamin A levels. Thus it would appear important to improve the diet of a considerable segment of the population or provide a vitamin A supplement for them.

Vitamin A is found in food in carotenoids, which are converted to vitamin A in the intestine; or, it may be preformed, as in foods from animal sources (or in diet supplements). There is no danger of excessive intake of vitamin A when carotenoids are ingested.

The recommended daily allowances of vitamin A are: for infants and children up to age 12 years, from 1,500 to 4,500 I.U.; for adults, 5,000 I.U.; and for pregnant women 6,000 I.U.[3,4] Although diets of many individuals provide higher levels of vitamin A, there are no known advantages in exceeding these allowances in normal individuals.

Thus, for prophylactic use or as a safeguard against inadequate intake, there are properly formulated supplements available on the market, i.e., those that contain 1,500 to 4,000 I.U. for infants and children, 5,000 I.U. for adults, and 6,000 I.U. for pregnant women.

However, excessive intake of preformed vitamin A may result in serious and potentially toxic effects. The easy availability of vitamin A in large doses without prescription exposes individuals to the danger of severe clinical toxicity. Physicians should be aware of the circumstances in which vitamin A toxicity may occur and its clinical manifestation.

Doses of 25,000 I.U. or more of vitamin A, which are present in some vitamin preparations, should not be used, unless severe deficiency of vitamin A, documented by an abnormally low blood level, exists. These doses taken daily for an extended period of time pose a risk, particularly to the pregnant woman and fetus. Studies in pregnant animals have shown that large doses of vitamin A produce central nervous system anomalies with hydrocephalus, encephalocoele, and other teratological effects in the offspring.[5,6] Infants may develop a bulging fontanel or hydrocephalus when given about 10 times the recommended daily allowance of vitamin A for several weeks.[7-9] The older child or adult with hypervitaminosis A manifests pseudotumor cerebri, a syndrome that may simulate the presence of an intracranial neoplasm, with signs and symptoms of unlocalized increased intracranial pressure,[10-18] such as headache, nausea, vomiting, lethargy, tinnitus, and diplopia. Physical findings are usually limited to the eyes, with sixth nerve paresis, papilledema, and, in long-standing cases optic atrophy and even blindness. Ingestion of as little as 25,000 to 50,000 I.U. of vitamin A per day for as short a period as 30 days can induce signs of increased intracranial pressure. Nonspecific findings encountered at all ages include dry skin and mucous membranes, sparse hair, brittle nails, myalgia, bone pain, arthralgia, abdominal pain, splenomegaly and hypoplastic anemia with leukopenia.

Despite awareness of the potential dangers of vitamin A toxicity, the incidence of hypervitaminosis A appears to be increasing. Hypervitaminosis A may result through

* Proceedings of Workshop on Vitamin A. Food and Nutrition Board, January 28, 29, 1971. To be published.

easy availability of high potency vitamin preparations without prescription and by the overzealous parent who frequently administers vitamins under the popular premise, that, if one is good, two are better. The problem may be compounded by the use of bizarre, highly fortified health foods.

Serious problems of hypervitaminosis A have arisen in the use of large doses of vitamin A in treatment of acne vulgaris in adolescents. The clinical impression that high doses of vitamin A (50,000 I.U. to 150,000 I.U. per day) over a prolonged period are beneficial treatment for acne vulgaris has not been validated by well controlled clinical trials, nor is the rationale for this method of treatment clear.[19]

Vitamin supplements with proper levels of vitamin A for infants, children, adults, and pregnant women are available on the market. These should be prescribed when indicated. Vitamin supplements containing more than the daily doses recommended (6,000 I.U.) should not be used.

## CONCLUSION

The grave risks resulting from the unrestricted sale of high concentrations of vitamin A make it imperative that an active curb, by appropriate legislation if necessary, be placed on the over-the-counter marketing of *high potency* vitamin A preparations. Physicians should be aware of the vitamin A content in the preparations they prescribe for their patients. They also should caution parents regarding the dangers of overdosage of this vitamin.

Committee on Drugs
SUMNER J. YAFFE, M.D., *Chairman*
Committee on Nutrition
L. J. FILER, JR., M.D., *Chairman*

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D-26

# THE EFFECT OF VITAMIN D ON LINEAR GROWTH IN INFANCY

## II. The Effect of Intakes Above 1,800 U.S.P. Units Daily

P. C. Jeans, M.D., and Genevieve Stearns, Ph.D.
Iowa City, Iowa

ALTHOUGH a large quantity of data concerning growth of infants must be analyzed in order to determine standard rates of growth, much can be learned by [illegible] groups of infants, living u[illegible] and diet. During the pe[illegible] fants has been so watched [illegible] greater part of the first [illegible] fants the major difference[illegible] to the source and quantit[illegible] necessarily involved also a

The first publication o[illegible] a good diet containing ap[illegible] cod-liver oil,* grew at rates[illegible] recent literature.[1, 2] It [illegible] dietary regimen but obtai[illegible] 135 units to the quart, g[illegible] standards. These standar[illegible] than the averages reporte[illegible] that vitamin A was not th[illegible] the increased rate of ske[illegible] D. These findings were [illegible] workers[3] in a well-contro[illegible] infants.

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In a study of a large [illegible] as being relatively unin[illegible] variants may lead to er[illegible] known that tall babies to[illegible] cm. long at birth will gr[illegible] average,[4, 5] but the avera[illegible]

From the Department of Pediatrics, State University of Iowa.
This study was aided by grants from Mead Johnson & Company, Evansville, Ind., and National Oil Products Company, Harrison, N.J.
*The term units throughout this article refers to U.S.P. units.





birth is only 22 cm. If the infants of a small group are predominantly either large or small, the growth results must be interpreted accordingly.

Illness also influences the rate of growth in length. In our experience, illness seems always to cause a slowing of growth, but the retardation may be of short or long duration, may occur during the illness, or after the infant has recovered. This period of slower growth is usually followed by a period of more rapid growth, which usually compensates entirely for the earlier slowing. Curves illustrative of these differing effects of illness on growth rate are shown in Fig. 1. The solid lines indicate periods of health, the dotted lines show acute illness, and broken lines a mild middle ear infection. The fine lines represent average [illegible] that following

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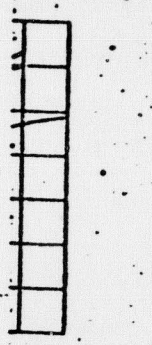

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# THE EFFECT OF VITAMIN D ON LINEAR GROWTH IN INFANCY

## II. The Effect of Intakes Above 1,800 U.S.P. Units Daily

P. C. Jeans, M.D., and Geneviève Stearns, Ph.D.
Iowa City, Iowa

ALTHOUGH a large quantity of data concerning growth of infants must be analyzed in order to determine standard rates of growth, much can be learned by following carefully the growth rates of small groups of infants, living under controlled conditions as to environment and diet. During the past few years a group of normal infants has been so watched and studied that for the greater part of the first year of life the variations in growth of infants the major differences in the rate of growth can be attributed to the source and quantity of the vitamin D intake. Other factors necessarily involved also are discussed.

The first publication of this series[1] showed that infants receiving a good diet containing approximately 1,800 units of vitamin D (as cod-liver oil,* grew at rates which were above the standards given in recent literature.[2,3] It was also shown that infants receiving the same dietary regimen but obtaining their vitamin D from irradiated milk containing 135 units to the quart, grew at rates which were below the accepted standards. These standards were based largely on data which showed no more than the averages reported in the present study. The earlier study showed that vitamin A was not the limiting factor in the diet which was responsible for the increased rate of skeletal growth of infants receiving irradiated milk containing D. These findings were confirmed by Macy and her associates[4] in a study of other workers' in a well-controlled group of infants.

The present report discusses the growth of infants receiving 1,800 units of vitamin D and the growth rates of individuals receiving more than 1,800 units. The data on the group of infants given 1,800 units have been published previously.[1]

In a study of a large group of infants, the rate of growth in length is considered as being relatively unaffected by the usual dietary factors. Only extreme variants may lead to error in the use of this measurement. For example, it is known that tall babies tend to remain tall throughout infancy. Babies 55 cm. long at birth will grow more rapidly than those 45 cm. long, on the average,[2,3] but the average rate of growth in length of infants of a small group is not affected by the average length at birth. Thus, if the average length at birth is 50 cm. for a group of infants, the average rate of growth in length will be the same as that for a group in which the average length at birth is only 22 cm. If the infants of a small group are predominantly either large or small, the growth results must be interpreted accordingly.

Illness also influences the rate of growth in length. In our experience, illness seems always to cause a slowing of growth, but the retardation may be of short or long duration, may occur during the illness, or after the infant has recovered. This period of slower growth is usually followed by a period of more rapid growth, which usually compensates entirely for the earlier slowing. Curves illustrative of these differing effects of illness on growth rate are shown in Fig. 1. The solid lines indicate periods of health, the dotted lines show acute illness, and broken lines a mild middle ear infection. The fine lines represent average growth for infants of the [illegible] that following

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# THE EFFECT OF VITAMIN D ON LINEAR GROWTH IN INFANCY

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Although a large quantity of data concerning growth of infants must be analyzed in order to determine standard rates of growth, much can be learned by following carefully the growth rates of small groups of infants, living under carefully controlled conditions of housing and diet. During the past ten years the growth of more than 100 infants has been so watched, many of the infants being studied during the greater part of the first year of life. For a large number of these infants the major differences in the dietary regimen have been in respect to the source and quantity of the vitamin D supplement, changes which necessarily involved also alterations in the vitamin A intake.

The first publication of this series[1] demonstrated that infants given a good diet containing approximately 340 units of vitamin D daily from cod-liver oil,[6] grew at rates faster than the averages reported in the recent literature.[2, 3] It was shown also that infants given the same dietary regimen but obtaining all their vitamin D from milk containing 135 units to the quart, grew at rates average by the above mentioned standards. These standards, in turn showed rates of growth more rapid than the averages reported in 1920 or earlier.[4] The evidence indicated that vitamin A was not the important factor, and it was concluded that the increased rate of skeletal growth was due to the effect of vitamin D. These findings were subsequently confirmed by Slyker and co-workers[5] in a well-controlled outpatient study of a large number of infants.

The present report discusses factors affecting the interpretation of growth rates of individual infants and extends the study to include a group of infants given from 1,800 to 4,600 units of vitamin D daily.

In a study of a large group, individual variants may be disregarded as being relatively unimportant. In studies of small groups, these variants may lead to erroneous conclusions. For example, it is well known that tall babies tend to grow faster than short ones. A baby 55 cm. long at birth will grow 27 cm. during the first year if his growth is average,[2, 3] but the average increase in length of a baby 45 cm. long at birth is only 22 cm. If the infants of a small group are predominantly either large or small, the growth results must be interpreted accordingly.

Illness also influences the rate of growth in length. In our experience, illness seems always to cause a slowing of growth, but the retardation may be of short or long duration, may occur during the illness, or after the infant has recovered. This period of slower growth is usually followed by a period of more rapid growth, which usually compensates entirely for the earlier slowing. Curves illustrative of these differing effects of illness on growth rate are shown in Fig. 1. The solid lines indicate periods of health, the dotted lines show acute illness, and broken lines a mild middle ear infection. The fine lines represent average growth for infants of the given age. It will be observed that following

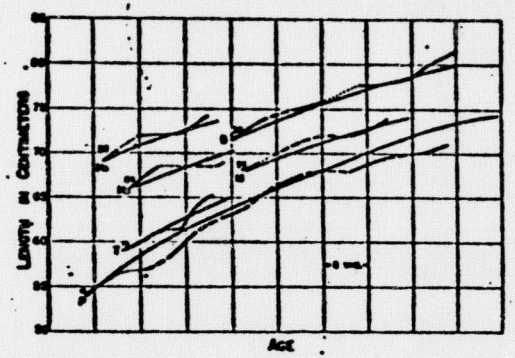


Fig. 1.—The effect of illness upon rate of growth in infancy. The solid lines indicate periods of health; dotted lines, acute illness; broken lines, mild chronic illness, usually otitis media. The age of each infant in weeks is given in numerals at the beginning of the curve, and fine lines represent average growth rate of infants of the given age.

an attack of acute bronchitis of two weeks' duration, the growth of infant IIa completely ceased for a period of four weeks; a similar cessation of linear growth was observed in infant B after acute laryngitis requiring tracheotomy. Both infants subsequently compensated entirely for the temporary slowing of growth. Bronchitis followed by mild middle ear infection caused cessation of growth for six weeks in infant IIo. On the other hand, acute bronchitis in infant T and pneumonia in infant P, both young infants, caused a slowing of growth for only about two weeks, while bronchitis followed by middle ear infection caused little or no slowing of growth until after seven weeks of illness for infant M. The last named infant resumed growth as soon as he recovered from the middle ear infection. The entire growth curve of infant P illustrates the fact that a chronic low-grade middle ear infection may have a far

From the Department of Pediatrics, State University of Iowa.
This study was aided by grants from Mead Johnson & Company, Evansville, Ind., and National Oil Products Company, Harrison, N. J.
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more marked and lasting effect on the growth rate than a single acute illness of much greater severity. In order to judge the effect of nutrition on the growth of a baby who has been ill, the growth rate should be followed for a sufficient period after illness to include both the compensatory period of more rapid later growth and also a period wherein growth occurs at the baby's normal rate.

Detailed and careful observation of infants under controlled conditions often indicates an apparent lack of relationship between the rate of growth during the first six to eight weeks of infancy and the dietary regimen given the infant. Fig. 2 shows the growth rates of three infants given as the sole source of vitamin D milk containing 135 units to the quart. Curves A and B indicate a steady rate of growth; curve C shows a much more rapid growth rate until the eighth week of life, after which this growth curve parallels the other two. All three infants were given the same dietary regimen throughout. The growth

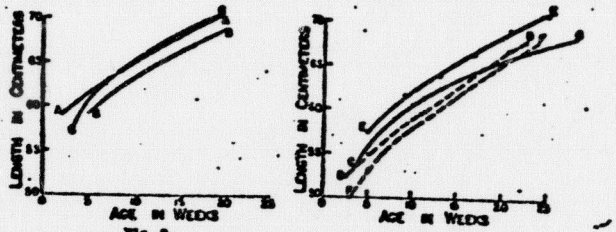


Fig. 2.




Fig. 3.

Fig. 2.—Growth rates of three infants given milk containing 135 units of vitamin D to the quart as the sole source of the vitamin. The growth rates of all three infants were similar after 8 weeks of age; the rapid earlier growth of infant C indicates the influence of factors other than diet.

Fig. 3.—Growth rate of infant C (Fig. 2) compared with those of three infants given 340 units of vitamin D daily as cod-liver oil. Curves D, E, and F show parallel growth rates after eight weeks, at a rate more rapid than the growth of infant C who received the lower voltage of vitamin D. Curves C, E, and F show rapid early growth, apparently not related to dietary regimen. Curves C and D illustrate the erroneous conclusions which may be drawn when only two measurements of growth are considered; actual rates of growth of the two infants are equal at 18 weeks of age; the growth of infant C is influenced by two factors, that of infant D apparently by only one.

of infant C after eight weeks shows that, throughout the entire period of infancy, his growth rate would probably approximate that of the other two infants. A short term study of this infant, particularly if measurements were taken only at the beginning and end of the study, might lead to very erroneous conclusions concerning the efficacy of the diet.

Fig. 3 shows the growth curve C in contrast to growth curves of three infants given 340 units of vitamin D daily as cod-liver oil. It will be noted that curves E and F show rates of growth previous to eight weeks which are more rapid than during the later period, whereas the growth



rate illustrated in curve D is consistent throughout. After the eighth week, the rates of growth of the three infants given 340 units of vitamin D daily (curves D, E, and F) are very similar and noteworthily greater than the rate of growth of infant C, who was given milk containing 135 units of vitamin D to the quart. A comparison of curves C and D illustrates the error which might easily arise if growth rates of curves C and D were compared only at first measurement and at or near the eighteenth week of life. Such comparison would show equal growth which might be wrongly ascribed to diet. While growth of the two infants is actually equal up to the eighteenth week the growth rate of infant C is the resultant of two factors; that of infant D is apparently affected by only one. Both infants C and E, on the other hand, show rapid early growth. The two curves are approximately parallel to the eighth week, but thereafter the rate of growth depends directly upon the dietary regimen. It seems, therefore, safer when studying growth of individual infants in relation to dietary regimen to consider only the rate of growth after the eighth week of life although the regimen should be instituted as soon after birth as possible.

We are as yet unable to state exactly the cause of these differing rates of growth during the first two months. In the few cases wherein accurate dietary and medical histories of the mother could be obtained, the rate of growth of the infant during the first two months correlated well with the nutritional and physical status of the mother at the time of the child's birth.

In studying the rate of growth of infants given large amounts of vitamin D, the entire growth curve of each infant is presented, but only the part of the curve after the eighth week of life is considered indicative of the effect of diet.

In this study vitamin D was given from three sources, two of which contained also vitamin A. A high unitage cod-liver oil* was given two infants in the amount of three standard teaspoonfuls daily, which allowed an intake of about 1,800 units of vitamin D and 6,300 units of vitamin A. A cod-liver oil concentrate emulsified in cream† was used as the second source; 3 c.c. were added to the daily feedings of each of three infants, permitting a daily intake of 2,200 units of vitamin D and 1,400 units of vitamin A dispersed in the milk. During the last three weeks of the study the vitamin A content of the concentrate was increased tenfold, allowing 14,000 units daily, the vitamin D content remaining constant. Viosterol in oil was given to four babies in amounts allowing about 4,500 units of vitamin D daily; this group of infants received no vitamin A in addition to that of the food. The studies were carried out without regard to season, and during the summer months

*Obtained through the courtesy of Mead Johnson & Company, Evansville, Ind.
†Obtained through the courtesy of the National Oil Products Company, Harrison, N. J.

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the infants were outdoors when weather permitted. While the group studied is small in number, the degree of dietary control was excellent, and the growth rates observed differed consistently from those of infants fed 300 to 400 units of vitamin D daily.

The growth rates of the infants are shown in Figs. 4, 5, and 6 in comparison with the Kornfeld standard curves as background. Fig. 4 shows the linear growth of two girls, one given cod-liver oil (1,800 units of vitamin D daily), and the other viosterol (4,000 units of vitamin D daily). Neither child showed extremely rapid growth during the first two months; both grew consistently faster than the average rate until 20 to 25 weeks of age. At that age a short period occurred wherein growth ceased entirely, after which linear growth was resumed at a rate

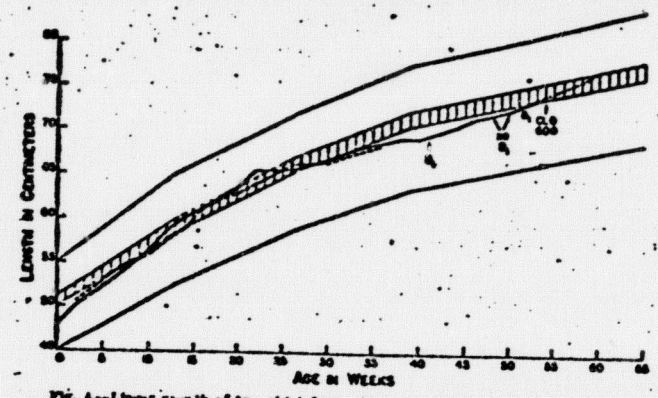


Fig. 4.—Linear growth of two girl infants given very high vitamin D dosage. The fine lines represent the average rates of growth by the Kornfeld standard. Baby B received 1800 units daily as cod-liver oil; Baby S was given 1600 units a day as viosterol. The period is weeks the term of thiamin therapy. The dotted line shows the growth rate when the vitamin D dosage was decreased to 600 units as cod-liver oil; rate of growth increased. (Broken line, Baby B; solid line, Baby S.)

below the average normal. Infant S who received viosterol was studied under this regimen until 40 weeks of age. As some decrease in appetite had been observed, thiamin (vitapin $B_1$) was added to the daily diet in the form first of an extract of rice polishings, later in a form combined with the carbohydrate (a dextrin-maltose mixture) of the milk feeding. Some increase in growth rate followed, but as both forms of the vitamin addition proved laxative, necessitating rest periods, the use of the thiamin addition was discontinued and the vitamin D dosage was changed to one teaspoonful of cod-liver oil, containing about 600 units of vitamin D. Growth was maintained at greater than average rate for a period of six weeks, when the study of the infant was concluded.



The second infant (B) whose growth rate is shown in Fig. 4, was given three teaspoonfuls of cod-liver oil daily, permitting an intake of 1,800 units of vitamin D and 6,300 units of vitamin A. This infant also showed evidence of decreased growth after about 6 months of age. The study of baby B could be continued only until the thirty-sixth week of age; the feeding instructions at discharge allowed only one teaspoonful of cod-liver oil daily. The baby visited the ward on her first birthday. At this age she was considerably taller than baby S., who was the same age. As will be seen from the chart, the two were of almost identical height at 36 weeks of age. The rate of growth of baby B, therefore, must have been above normal after the vitamin D dosage was decreased.

Four other girl infants have been studied (Fig. 5), but only one could be studied throughout the major part of infancy. This infant (Ba) had been used as a subject for a study of the effect on growth and

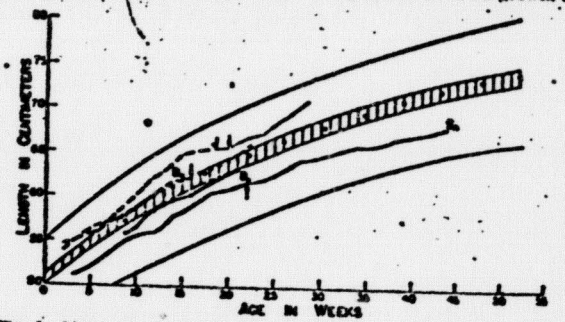


Fig. 5.—Linear growth of four girl infants given very high vitamin D dosage compared to standard Kornfeld rate. Dotted portions of curves represent growth rates observed when the vitamin D dosage was decreased to 400 units daily as cod-liver oil. Babies Ba and J were given 2200 units of vitamin D daily as the cod-liver oil concentrate dispersed in the feeding; growth increased when the dosage was decreased to 400 units daily. Baby Ba was given 1600 units daily as viosterol. Baby Ba was given 270 units daily as viosterol until 21 weeks of age, at which time the dosage was increased to 4600 units. The slowing of growth with high dosage contrasts with the increase of growth rate of baby J when the vitamin D intake was lowered. The circles represent average heights observed by Pratman and Higgons' for girl infants given 1600 to 2000 units of vitamin D daily.

mineral retention of a vitamin D intake of 270 units daily as viosterol. That study had been discontinued in the spring and the baby, then 21 weeks old, was thereafter given 4,600 units of vitamin D as viosterol. The rate of growth to 21 weeks had been average; after this period, the rate was considerably below average, remaining so throughout the study. The failure of the high vitamin D dosage to increase growth rate is in contrast to the increase in growth rate noted in baby S when 600 units of vitamin D were substituted for 4,600 units.

Baby Ba was given 4,600 units of viosterol daily from the date of her admission at the age of 9 weeks. At 21 weeks, the baby left the hospital.

Growth was about 1 cm. greater than the average rate and had not yet showed evidence of slowing, a result similar to those observed with Infants S and B at the same age.

Two girl infants were given the "high vitamin D milk" made in the laboratory by adding to each day's feeding enough cod-liver oil concentrate dispersed in cream to give a total day's intake of 2,200 units. These infants could be studied for less than six months. No decrease in appetite was observed. One infant, Br, grew at a little less than average rate at the beginning of the study, and at average rate after the age of eight weeks. The growth of the other baby, J, was faster than average from the eighth to the fifteenth week, then showed a definite slowing for the succeeding five weeks. The vitamin D intakes of both infants

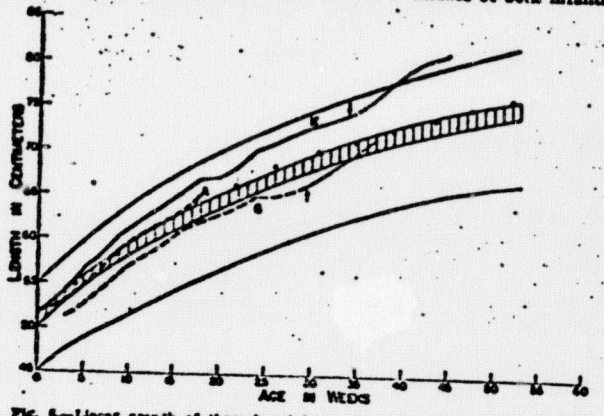


Fig. 6.—Linear growth of three boy infants given very high vitamin D dosage compared to standard Kornfeld rate. Dotted portions of curves represent growth rates observed when the vitamin D dosage was decreased to 400 units daily as cod-liver oil. Baby G received 2,200 units daily as the cod-liver oil concentrate dispersed in the formula; Baby A, 1600 units daily as cod-liver oil concentrate dispersed day as observed. The rates of growth of babies G and K were increased when the vitamin D intake was decreased to 400 units a day. The circles represent average lengths observed by Hutchison and Hargreaves for boy infants given 1600 to 3000 units of vitamin D daily.

were then changed to 400 units daily as cod-liver oil. Subsequent growth is shown as dotted lines. Baby J showed average growth for four weeks, then sharply accelerated growth for the succeeding four weeks. Baby Br's growth was maintained at average for four weeks, and then the rate increased somewhat.

The growth rates of the three boy infants are shown in Fig. 6. The lowest curve, G, indicates the growth of the baby given 2,200 units of vitamin D in the milk, as the cod-liver oil concentrate dispersed in cream. Growth proceeded at better than normal rate until 16 weeks



of age and from then to 24 weeks at barely normal rate. After the twenty-fourth week growth was definitely slowed. At 29 weeks of age the high vitamin D feeding was discontinued, and 400 units of vitamin D as cod-liver oil were given daily. The growth rate showed an almost immediate increase, which was maintained for a period of six weeks, until the study was concluded.

A second boy, A, was given 1,800 units of D daily as cod-liver oil. This baby left the hospital at 18 weeks of age, before any slowing of growth was observed. The child's appetite was excellent throughout the study.

The third boy, K, was remarkable for his excellent appetite throughout the entire study. His food intake was always above average. His rate of growth was excellent up to 24 weeks of age, except for one temporary slowing due to an upper respiratory infection. From the twenty-fourth to the thirty-fourth week growth continued at average rate. Slowing of growth in this child could not be considered as due to decreased ingestion of food caused by lack of appetite. The child's hands and feet were very large compared to his body size, so that, even though the baby's length was above average, it was felt that stunting might have occurred. The vitamin D dosage was therefore decreased to 400 units daily, given in the form of cod-liver oil. After two weeks the growth rate increased, and in ten weeks the baby length had increased 6.6 cm. or 3.2 cm. above the expected increase of 3.4 cm. in this period.

Summarizing, each infant given the high D dosage and studied up to 25 weeks of age or longer showed a slowing of growth to or below average rate by the standard used. Each of these infants who was then given a lower dosage of vitamin D, 400 to 600 units daily, showed an increased rate of growth, four of the five growing at markedly greater than average rates for periods of four to ten weeks.

In some of the infants the decrease in rate of growth observed when the very high dosage of vitamin D was given could be ascribed to decreased appetite with consequent food refusals; other infants, however, showed excellent appetites throughout the study, but the growth rate could still be increased by decreasing the daily vitamin D ingestion. The depression of appetite occurred as often when the vitamin was given in concentrated form, as when it was ingested as three teaspoonfuls of oil.

Four infants were given no vitamin A in addition to that of the food; of these, two grew at less than average rate and one at average rate during later infancy, while the study of the fourth was concluded at twenty-one weeks, at which time she was growing at average rate. Two of these babies were later given cod-liver oil containing 400 and 600 units of vitamin D, 2,800 and 4,200 units of vitamin A, respectively. Both babies showed a definite increase in rate of growth.

Two babies were given three teaspoonfuls of cod-liver oil, containing 12,000 to 13,000 units of vitamin A in addition to that of the food. One baby grew at less than average rate after 23 weeks of age; at 34 weeks of age the cod-liver oil dosage was decreased to one-third of its former level, thus decreasing the intake of both vitamins A and D; growth proceeded more rapidly. The second infant was studied only to 18 weeks of age; the rate of growth was above average at that age.

Three babies were given 1,400 units of vitamin A daily in addition to that of the food. During the last few weeks of the vitamin D study the vitamin A content of the diet was increased tenfold, the vitamin D ingestion remaining constant. The growth rate of two of the three infants continued to decrease, that of the third remained approximately the same. When the vitamin D intake was decreased to 400 units daily and the vitamin A intake to 2,800 units, the rate of growth increased for all infants.

Of the five infants studied to thirty weeks or later, four presented a very definite slowing of growth, one grew at average rate. The infant who grew at average rate and two of those whose growth rate was below average received no vitamin A in addition to that of the food. One infant whose later growth was below average, received 6,300 units of vitamin A in addition to the vitamin D; her rate of growth was practically identical with that of one of the infants given no added vitamin A. The fifth infant was given a tenfold increase in amount of vitamin A for three weeks of the study without any observable increase in growth rate occurring, in contrast to the prompt increase in growth rate when the vitamin D intake was lowered. Thus, the slowing of growth, when observed, was noted in infants given additional vitamin A or only that of the diet. The increased rate of growth which followed the lowering of the vitamin D intake occurred whether the vitamin A intake was lowered markedly or increased. Vitamin A, in amounts above those supplied by the food, apparently does not affect linear growth in infancy.

The study of these nine infants indicates that when vitamin D is fed to infants in amounts over and above 1,500 units daily, growth proceeds at average or greater rate up to about 6 months of age, and that after 6 months of age, increase in length occurs at average or less than average rate. The rate of growth with very high vitamin D dosage is thus about the same as had been observed for sixteen infants given vitamin D milk containing only 135 units to the quart, and is definitely slower than the growth rate observed in thirty-six infants given 340 units of D daily.

Very similar results in growth rate with high vitamin D intake are reported in a large outpatient study by Pratman and Higgons.[6] These authors report growth rates of 1,112 subjects (577 boys and 535 girls)



of whom 60 per cent came from the middle or wealthy classes. The infants were of American parentage, with northern European stock predominating. The dietary regimen was very carefully supervised and included vitamin D as follows: "Cod-liver oil or one of its substitutes is started at four weeks. By two months each child receives daily 2,000 or more units of vitamin A (U.S.P. XI) and 1,600 or more units of vitamin D (U.S.P. XI). At 4 months this dose is increased to a minimum of 20,000 units of vitamin A and 3,200 of vitamin D. After 8 months the amount varies from this minimum to a maximum of three times this quantity, depending on the condition of the child."

The average lengths observed by these investigators are shown in charts 5 and 6 as circles. It will be noted that the average growth rate for the boys is almost identical with the "upper average" line of the Kornfeld standard, and for the girls, exactly average according to the standard. That average growth was achieved by the outpatient group and less than average growth was observed for many of the infants of the present study may be attributed to the better degree of control always possible in inpatient studies. The data presented by Pratman and Higgons thus support admirably the data presented in this paper.

The effect of vitamin D on linear growth apparently reaches a maximum and further increases in intake result in decreased, rather than increased rates of growth. The rate of growth of infants given 135 unit vitamin D milk is greater than that of infants given no vitamin D;[2,3] infants given 340 units[4] or 600 units[5] of vitamin D daily grew at noteworthily greater rates than those receiving only 135 units. No definite difference in growth rate appeared between the groups given 340 and those given 600 units of D daily. Infants given very high dosage of vitamin D (1,500 to 5,000 units daily), however, grew at rates definitely less rapid than those given 340 to 600 units, and approximately equal to those of the group fed milk containing 135 units to the quart. A few infants given these high dosages grew no faster than infants receiving no additional vitamin D.[6,8]

This study of growth of infants with a high intake of D brings out an additional factor which must be considered in studying the growth of individuals, namely, that some factors of diet definitely affecting growth may not show a noticeable effect until the infant is more than 6 months of age. In order to determine the effect of a given dietary regimen upon the rate of growth and development of the infant, it appears necessary to study the infants throughout the greater part of the first year of life.

## SUMMARY

The rate of linear growth of nine infants given from 1,500 to 4,600 units of vitamin D daily has been compared with standard rates of growth, and with the growth of infants given the same dietary regimen

but amounts of vitamin D varying from 133 to 340 units daily. The rates of growth with the very high vitamin D intake were similar to or less than those of infants given 135 units daily, and definitely lower than the growth rates of infants given 340 units of vitamin D daily.

It is concluded that the effect of vitamin D on increasing linear growth reaches a maximum when the vitamin D intake is greater than 135 and less than 1,800 units, probably in the neighborhood of 340 to 600 units daily.

Vitamin A in amounts exceeding those of the food (milk, vegetable, and fruit purées) apparently does not affect linear growth of infants.

Factors affecting growth rates of individual infants are discussed. It is concluded that in order to determine the effect of the dietary regimen, growth should be studied well past 6 months of age, preferably during the greater part of infancy. Growth during the first 9 weeks of life may be affected by factors other than the dietary regimen of the infant.


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# ENCEPHALITIS RHEUMATICA
## (CHOREA MINOR OF SYDENHAM)
### Its Diagnosis and Course


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St. Louis, Mo.


*INTRODUCTION.*—Chorea continues to be a disease of great pediatric interest and discussion because of its frequency of occurrence, and its uncertain etiology and relation to rheumatic fever. Because of the nature of the condition there is great difficulty in securing direct evidence of its cause, course, and relationship. It is the purpose of this paper to discuss, first, the concept of the disease formed from an experience during the past twenty years at the St. Louis Children's Hospital, in the Children's Cardiac Clinic, and, second, to describe the common conditions occurring in pediatric practice which simulate the disease and may be confused with it.

Dr. Marriott was always interested in each case of chorea on the wards and stimulated others about him in the subject. Probably the elusive, unknown, uncertain features challenged his scientific mind to search for something new.

*History.*—Since Sydenham's original description of chorea[1] in 1686, very little important information has been added. Cheadle[2] pointed out clearly and definitely the close relationship between chorea and rheumatism in children and probably was the first to emphasize the peculiar manifestations of rheumatism in children as compared with adults. His description of chorea supplements Sydenham's with accurate clinical observations based on principles of modern medicine. Since Cheadle's work nothing has been added to our knowledge.

Pathologic reports are extremely meager, there being no mention of the disease in most text books of pathology. Clinical studies and reports of importance during the past twenty years come from either neurologists and psychiatrists,[3-6] with emphasis on the symptoms and relation to other types of incoordinate movements of children, or from pediatricians,[7, 8, 9] and cardiologists,[10-12] with more emphasis on the relation of the disease to the rheumatic state and its manifestations elsewhere in the body. These reports describe less the symptoms and more the underlying cause of the disease, the widespread lesions of rheumatism in children, and the high incidence of heart disease in the general group. Many of these reports are concerned with the direct relationship


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Dr. Rice-[illegible] regret [illegible] unemployed [illegible] mild cases [illegible] efferent [illegible] of the colon [illegible] uld these [illegible] a degenerative [illegible] the appendix [illegible]r. Goligher [illegible] ld cases. Hist[illegible] ulcerative colit[illegible]r.

the pathologic[illegible] ecount its [illegible] ndency to spo[illegible] cure, and [illegible] and for certa[illegible] w is a very cle[illegible] ma of the skin [illegible] was confined [illegible] although [illegible] subjected wou[illegible] he vulnerabilit[illegible] ity of secondar[illegible] s of eczematid[illegible]

J. NAISH.

correspon[illegible]ence between [illegible]brooke between [illegible] proctitis whi[illegible] gnition, as d[illegible]ve colitis in [illegible]olitis, relapsin[illegible]er of the rectum[illegible] each form [illegible]ful; but surel[illegible]y the same.

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modern disease [illegible] the very one[illegible] bowel are still [illegible]th, if necessary, [illegible]a of the patient. [illegible]lso the patient [illegible] I have seen a [illegible]ease whose life [illegible]ed in this way [illegible]aled. What is [illegible]chiatry in the [illegible]in the hospital [illegible]f these patients [illegible]g than removing [illegible]pproach is not

[illegible]ble for intensive [illegible]t, in an attempt [illegible]n between the [illegible]nd the colon;

[illegible], 69, 8.

a successful issue may well bring colitis, as Dr. Rice's prophesies, once more under the ægis of physician. Meanwhile, when the changes in the are deemed irreversible or the patient's life is in [illegible], the best chance of restoring health is by radical [illegible]ery, undertaken as soon as possible. The thought[illegible] of surgeons in special centres, who have perfected [illegible]gical technique and improved the appliances for the [illegible]ent, has made ileostomy and excision of the colon [illegible]peration which offers the patient a safe, comfortable, [illegible] unrestricted life.

[illegible]ted.

D. LANG STEVENSON.

## RELIEF OF MENTAL HOSPITALS

SIR,—Dr. Atkin (July 4) seems to overlook the fact [illegible] a mental hospital is, to all intents and purposes, [illegible] institute for detention; and no separate units within [illegible] walls would alter that feature. Moreover, the time [illegible] every mental hospital will have such units is in the [illegible]ote future.

The need for relief is very acute in all parts of the [illegible]ntry; and we have to rely on buildings already [illegible]ding and staffed. At several general hospitals I [illegible]e found rooms unused. These rooms could be con[illegible]ted into units of the sort I have proposed; and, [illegible]e very many mental hospitals, they could work [illegible]thout having the full staffing described by Dr. Atkin [illegible] indispensable. Surely, too, the overcrowding of [illegible]tal hospitals is to a great extent due to admission [illegible]patients who should be in a general hospital.

I should have understood Dr. Atkin's reluctance [illegible]ter if he had been writing from a general hospital [illegible]ther than a mental hospital. We are, however, in full [illegible]greement on one point: like him, I believe that my [illegible]posal to set aside general-hospital beds for mental [illegible]ases is unlikely to get much immediate support [illegible]m other specialists. But I also believe that the time [illegible] come when it should be recognised that psychiatry [illegible]s no less than medicine plus the art of understanding [illegible] mind. Medicine has reached a point where it can get [illegible]le further without the aid of its crude but powerful [illegible] rapidly growing younger brother.

[illegible]ackton Mental Hospital,
[illegible]ickcote.

J. W. MULLNER.

## ANÆSTHESIA AND CLINICAL INVESTIGATIONS

SIR,—With the principle stated in your leading article [illegible]t week few would disagree. You say "that the only [illegible]ctor limiting the use of anæsthesia for this [pneumo-[illegible]ncephalography] and many other investigations that [illegible]ental distress should be the number of trained anæs[illegible]etists."

However, it is one thing to define a limiting factor, [illegible]d quite another to remedy it. Over a decade ago, I found that the duties of anæsthetist in a large teaching [illegible]ospital could be accomplished by a mixture of guess-[illegible]rk and common sense. Since that time it has become [illegible]lain that sheer practice and experience, however [illegible]xtensive, is not adequate without proper training.

To my mind, the most serious question posed by the [illegible]nsideration of anæsthetics and clinical investigation [illegible] that of training. Trained anæsthetists are not unduly [illegible]numerous; and senior anæsthetists, who alone can pass [illegible] their special skill, are even less numerous. One has [illegible]n the stiffening of the standards for anæsthetic [illegible]plomas—and rightly, for the responsibility carried by [illegible]e anæsthetist has increased very greatly. Experience [illegible]s shown that even after the potential anæsthetist has [illegible]n allowed time to become a reasonably experienced [illegible]sician, at least two years of uninterrupted training [illegible]d supervised work, solely in anæsthetics, is necessary [illegible]ore anæsthetics for clinical investigations should [illegible]e tackled.

Whereas at an operation, an experienced surgeon is [illegible]present (at least as counsel and companion in crisis), large parts of a clinical investigation may be entrusted to technicians. As a rule these technicians are well trained and qualified in their special task, but lack the broader background of clinical experience. The anæsthetic may be prolonged long after the removal, for example, of a lumbar-puncture needle. The anæsthetist may often find himself virtually alone to deal with dangers and difficulties, arising, not from the anæsthetic, but from the essential nature of the investigation. The better the anæsthetist, the more likely these are to occur; for good anæsthesia encourages thorough and methodical investigation, which takes a long time.

Investigation like this is greatly to the advantage of precise diagnosis, and anæsthesia is of real value, for the conscious patient simply cannot tolerate the ordeal of lengthy posturing. In addition, the anæsthetist may adjust the blood-pressure to assist the insertion of the needle in carotid or vertebral arteriography.

I, for one, would reject absolutely the idea that patients should go home after a long anæsthetic, whatever the agent. To persist in such a practice would, in my opinion, guarantee a collision with untoward circumstance—sooner or later. The first twenty-four hours after an anæsthetic belongs to the anæsthetist to follow up his case, and it should be claimed as a right. As there are rarely surgical considerations after such investigations, these cases offer particular scope for observation and clinical examination in the postanæsthetic phase.

Watford Maternity Hospital,
Watford.

J. NOEL JACKSON.

## IDIOPATHIC HYPERCALCÆMIA IN INFANTS

SIR,—"Marasmus," so named by our predecessors but a mystery to them, is no longer considered to be a single disease, and (as you noted some months ago [1]) many of the different conditions included under this general term have now been separated off. As we turn the fine adjustment of the diagnostic microscope, it is most important to avoid confusion in our new and, we hope, more accurate terminology. Confusion at any stage, especially at the beginning, can easily hinder progress; meticulous care must therefore be taken over nomenclature. Ideally each new disease name should indicate the ætiology; when this is not yet possible it should be accurately descriptive, preferably in terms of function and structure; failing this it must be simply clinical.

Attention is now being directed to a group of disturbances affecting infants in which chronic hypercalcæmia is present, not associated with overt poisoning by vitamin D or with hyperparathyroidism. The nomenclature used in the description of these cases of hypercalcæmia will not be easy until more is known about them and especially about their ætiology; for the moment we can only label these syndromes descriptively. One type of syndrome manifesting hypercalcæmia has been labelled by observers in England and in Switzerland, as follows:

> Generalised retardation, with renal impairment, hypercalcæmia, and osteosclerosis of skull. (One patient, described by Butler.[2])
>
> Chronic hypercalcæmia with osteosclerosis, craniostenosis, and cortical nephrocalcinosis. (One patient, described by Fanconi.[3])

Subsequently, these English and Swiss patients were more fully reported under the title "Chronische Hypercalcämie, kombiniert mit Osteosklerose, Hyperazotämie, Minderwuchs und kongenitalen Missbildungen" by Fanconi et al.[4]

Another syndrome occurs, more common than the first, which is more benign and shows a less distinctive

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clinical picture (anorexia, vomiting, wasting, constipation, thirst, polyuria, and sometimes dehydration); for this syndrome the term "idiopathic hypercalcæmia in infants with failure to thrive" has been suggested as a temporary descriptive label [5] and accepted as convenient by Payne.[6]

The interesting single case-report published by Dr. Creery (July 4) under the title "idiopathic hypercalcæmia of infants" is the first example of "generalised retardation with renal impairment, hypercalcæmia and osteosclerosis" to be described in *The Lancet*. In this case the features do not match those which characterise "idiopathic hypercalcæmia with failure to thrive," and they are typical of the syndrome described by the Swiss and British workers. It is therefore unfortunate that Dr. Creery did not use one of the labels already applied by these workers. It is important to make this point in order to prevent confusion arising at this stage of clinical description when our understanding is limited, since it is so difficult to change wrong names when once they have been published and indexed.

There are certain clinical features which serve to distinguish the cases of simple idiopathic hypercalcæmia of infants from those with general retardation and osteopetrosis.

(1) The simple hypercalcæmias are transient and benign, there is no peculiarity of the facies, no distinctive bone changes, no cardiac bruit, and probably no hypertension. It is probably significant that an associated renal acidosis is occasionally found, perhaps in about 1 case in 5. The serum-calcium is raised from about 12 mg. to 18 mg. per 100 ml.; and the blood-urea is usually raised to about 70 mg. per 100 ml. As a rule recovery begins to take place in a few weeks; coincidentally the blood chemistry returns to normal and the infant resumes its natural gain in weight. Afterwards the intelligence is apparently normal.

(2) The cases with osteopetrosis have skeletal changes resembling Albers-Schönberg disease. The chemical changes in the blood are similar to those of simple hypercalcæmia except that there may be a rise in the blood-cholesterol; apart from this, there is at present no other chemical method of discrimination. An important clinical sign is the presence of an impressive systolic murmur. There is no evidence that this is due to congenital heart-disease, as Dr. Creery (following Schlesinger et al.[4] postulates in his case; the systolic murmur is probably due to hypertension. Both mental and physical progress is much retarded in these cases and, although some general improvement takes place, the mental state usually remains poor in our experience. It seems too that the facial appearance may be characteristic: the mouth is very wide, the upper lid is often thick and deeply bowed, the mandible recedes, the ears are set low on the head, and the child looks ill-tempered and unhappy.

Although we believe that these two clinical pictures may be different syndromes, the reverse is possible. This is a problem to be solved by the study of many more cases and, in order to do this, future clinical reports should, as far as possible, give the following data:

(1) Clinical photographs demonstrating the facies both early and late in the progress of the disease.
(2) Radiographs showing the skeletal changes at different stages.
(3) Radiographs of the kidneys at different stages.
(4) Blood-pressure readings, preferably made by careful adherence to a well-recognised technique, such as the flush method.
(5) A follow-up report and estimate of the mental age.

We would be grateful to hear of any such cases which the clinician concerned does not himself wish to publish.

St. Mary's Hospital Medical School, London, W.2. REGINALD LIGHTWOOD
THOMAS STAPLETON.

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## N.H.S. PRESCRIPTIONS

SIR,—I have just received the Ministry of H. circular on Proprietary Preparations.[1] I wonder if I alone in thinking that this merely scratches at surface of the prescribing problem.

I would suggest that all drugs can be classified a large measure of agreement into two categories:

1. Those that have a proved therapeutic effect in cause disease processes (e.g., antibiotics) or controlling symptoms (e.g., hypnotics and antispasmodics).

2. Those that have no such proved effect and are largely as vehicles for suggestion (e.g., tonics).

It is arguable that only drugs of the first category irreplaceable therapeutic agents, and if free prescrip was limited to them it would make a very big in the drug bill. This need not limit the doc prescribing since the other drugs could be available the patient's expense; and in so far as they unessential it does not seem unreasonable that should be paid for.

However unpalatable it may be to vote-cat politicians, the scope of the health service must be limited by the funds available. At present a l proportion of these funds is being ineffectively app to provide unessential drugs. No action on the pa prescribing doctors will materially reduce this unless it is supported by an official declaration money available is for the free provision only of dr that have an agreed therapeutic value. A less ran field of free prescription must divert funds t other more effective measures in the fight aga disease.

Marlborough College, Wiltshire. T. A. A. HUNTER.

## VENOUS LIGATION AND POSTPHLEBITIC SEQUELÆ

SIR,—It would be unfortunate if the unqualified statement in the last sentence of the summary of the paper by Professor Boyd and his colleagues (July 4) should be too unreservedly accepted, and if it should discourage further cautious controlled investigation of this method of treatment.

Admittedly, the objective findings, as shown in the figures quoted for venous-pressure measurements, do appear to offer convincing proof that the operation fails to improve the venous return. Many workers, however, have found that the clinical results of the operation are very much more favourable than has been Professor Boyd's experience. Moore[2] recently reported 23 such cases, followed for from nine months to three years, and there was complete relief of symptoms in 18 of them, and in no case was there deterioration or undesirable side-effects.

The argument of Professor Boyd and his colleagues against major venous ligation in the treatment of chronic gravitational ulcer is greatly weakened by three facts: by their inclusion of 12 cases which had no ulceration, by the variety of levels at which the vein was tied, and by the large proportion of cases (the actual number is unspecified) in which the operation was combined with local excision and grafting of the ulcer. Few will agree that "femoral ligations are without doubt the least unsatisfactory"; indeed, most workers who have tried both have reached the opposite conclusion. The poor long-term results of any type of grafting operation in these legs have been a disappointment to many surgeons; and vein ligation cannot be fairly assessed if it is combined with an operation which has such notoriously poor late results.

The authors state—alarmingly—that 6 out of 15 patients whose popliteal veins were tied became mark

1. See *Lancet*, July 25, 1953, p. 196.
2. Moore, H. B. *Ibid*, 1953, i, 23.

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91-5
Repr. 16 cases
excellent. England. mild.

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# IDIOPATHIC HYPERCALCÆMIA IN INFANTS WITH FAILURE TO THRIVE

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Reporter C. Ring

MUCH interest has been aroused by the success of biochemical methods in the investigation of the wasted infant. This interest has been further stimulated by recognition of the syndrome of "idiopathic hypercalcæmia, with failure to thrive" (Lightwood 1952a), in which anorexia, vomiting, and constipation are associated with wasting, hypotonia, and elevation of the serum-calcium and blood-urea levels. Clinically the condition simulates infantile renal acidosis; the ætiology is unknown; and spontaneous recovery is the rule.

We here describe 16 cases seen in the Royal Belfast Hospital for Sick Children and the Ava Hospital during the period April, 1952 to June, 1954. 1 case previously reported (Creery 1953) of idiopathic hypercalcæmia with renal impairment, osteosclerosis, craniostenosis, hypertension, and general retardation (Fanconi and Girardot 1952, Schlesinger, Butler, and Black 1952) is not included, because it is at present uncertain what relation this type of case bears to the syndrome under review.

## Observations

### ÆTIOLOGY

*Sex.*—There were 11 females and 5 males in the series.

*Pregnancy and Delivery.*—Pregnancy was normal in 10 cases; in the remainder it had been complicated by considerable vomiting. There were 3 twin pregnancies, one twin from each pair (1 identical, 2 dissimilar) being affected. 5 of the infants were firstborn and 2 were premature. Delivery was normal in 10 cases and of unknown type in 1. There were 3 forceps deliveries, 1 breech, and 1 cæsarean section. 1 infant suffered neonatal asphyxia.

*Feeding Before Onset of Symptoms.*—5 infants were never breast-fed, 3 were breast-fed for less than a week, and 7 for less than four weeks. 1 infant was breast-fed for two months. Subsequent feeding in 15 cases was with dried milk fortified with vitamin D (7 were fed on full-cream dried milk, 6 on half-cream followed by full-cream milk, and 2 on half-cream milk alone). 1 infant was fed on liquid cow's milk. In several cases mixed feeding had started.

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*Vitamin D Before Onset.*—2 infants did not have vitamin-D supplements. The remainder had supplements varying from 400 to 1600 international units (I.U.) daily; the majority had a daily dose in the region of 800 I.U. An attempt has been made to assess the approximate total vitamin-D intake from a consideration of the known diets and vitamin additions. From this it would appear that 2 infants had about 700 I.U. daily, 6 had 1100–1600, 7 had 1800–2400, and 1 had 3200.

*Preceding Alkali Therapy.*—7 infants had varying but regular dosage with alkali preparations: 3 had magnesia in some form and 4 had alkaline carminative mixtures.

*Preceding Illness and Therapy.*—A preceding gastro-enteritis was noted in 2 cases. In 1 of these infants this was associated with pyelonephritis and otitis media. 1 infant was said to have had a severe common cold, 1 a sore throat, and 1 otitis media. In only 1 case was there a history of sulphonamide medication.

## THE CLINICAL PICTURE

These infants appeared to thrive at first and the onset of definite symptoms was usually clear-cut, at ages from six weeks to nine months (see table). In 1 infant, symptoms were present from birth. Vomiting—often unspectacular but occasionally severe and projectile—was the initial symptom in 8 cases, and it occurred in all but 1 of the 16. In 4 cases the illness began with constipation and in 3 with refusal to feed. In 1 case vomiting and constipation were noticed more or less simultaneously.

Vomiting tended to be most severe during the early part of the illness and gradually subsided. Periodic exacerbations occurred, but it ceased with the child's recovery. Constipation was obstinate in most cases, the stools being infrequent, small, and hard, and it resisted the household remedies which were given with remarkable perseverance. Proprietary alkali preparations were commonly used regularly (twice or thrice weekly) or daily for periods of weeks or months with a singular lack of success. 12 infants were given magnesia preparations, with or without additional alkaline carminatives or citrate. 1 received an occasional dose of carminative and 1 an occasional dose of magnesia; 2 had no alkali therapy. Other laxatives were frequently given without effect.

All the infants failed to gain weight normally, and some were 4–5 lb. below their expected weights. Definite anorexia was noted in 12 infants and distaste for solids was conspicuous. 11 of the mothers thought that their infants passed an excessive amount of urine. The mothers mentioned thirst in 6 cases, pallor in 5, and "muscular weakness" in 4.

Physical examination revealed little apart from wasting of varying degree. Growth in length appeared to be retarded in 4 of the 11 infants who were measured; head circumference was within normal limits and craniostenosis was not noted.

Despite their poor physical condition most of these infants were alert and contented, though some showed a curious apathy. This pleasant nature, associated with

## SUMMARY OF THE CASES

| Case no. | Age at onset (mos.) | Age at recognition (mos.) | Duration to clinical recovery (mos.) | Highest serum-calcium (mg. per 100 ml.) | Highest blood-urea (mg. per 100 ml.) | Follow-up | | | | Other remarks |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | Duration (mos.) | Last known serum-calcium (mg. per 100 ml.) | Last known blood-urea (mg. per 100 ml.) | Stature | |
| 1 | 1½ | 17 | 15 | 16 | 35 | 18 | 10·3 | 30 | Average | Mentally retarded (? not connected with illness) |
| 2 | 3 | 13 | 13 | 15·9 | 124 | 18 | 12·8 | 49·7 | Below average | Secondary rise in serum-calcium age 27 months |
| 3 | 9 | 12 | 4 | 13 | 33 | 12 | 8·7 | 33 | Below average | |
| 4 | 4 | 7 | 11 | 16·8 | 92·6 | 9 | 12 | 45 | Average | " |
| 5 | Birth | 17 | 22 | 12·3 | 39 | 6 | 11·2 | 30·3 | Average | " |
| 6 | 2 | 13 | 16 | 14·2 | 61 | 3 | 11·7 | 43 | Average height. Underweight | Urinary infection at follow-up |
| 7 | 6 | 12 | 8 | 13·8 | 43 | 5 | 10·6 | 46·4 | Slightly below average | Anæmic at follow-up (62%) |
| 8 | 7 | 14 | 14 | 12·5 | 46 | 1 | 11 | 28·5 | Average height. Underweight | Recurrent tonsillar sepsis |
| 9 | 3½ | 7 | 11 | 14·5 | 96 | 6 | 11·7 | 43 | Average height. Underweight | Anæmic at follow-up (66%) |
| 10 | 1½ | 6 | 7 | 13·1 | 52 | 6½ | 11·7 | 37·5 | Below average | |
| 11 | 5 | 11 | " | 14·5 | 80 | " | " | " | " | Lost sight of |
| 12 | 7½ | 7½ | 1 | 14·7 | 78 | 3 | 12·3 | 32 | Average | |
| 13 | 5 | 9½ | " | 14·4 | 98·5 | " | " | " | " | Remains in active stage |
| 14 | 6 | 11 | 6 | 14·1 | 46·4 | 1 | 11·4 | 36·4 | Average height. Underweight | |
| 15 | 8 | 10 | " | 17·3 | 100 | " | " | " | " | Remains in active stage |
| 16 | 5 | 8 | " | 17·5 | 103 | " | " | " | " | Remains in active stage |

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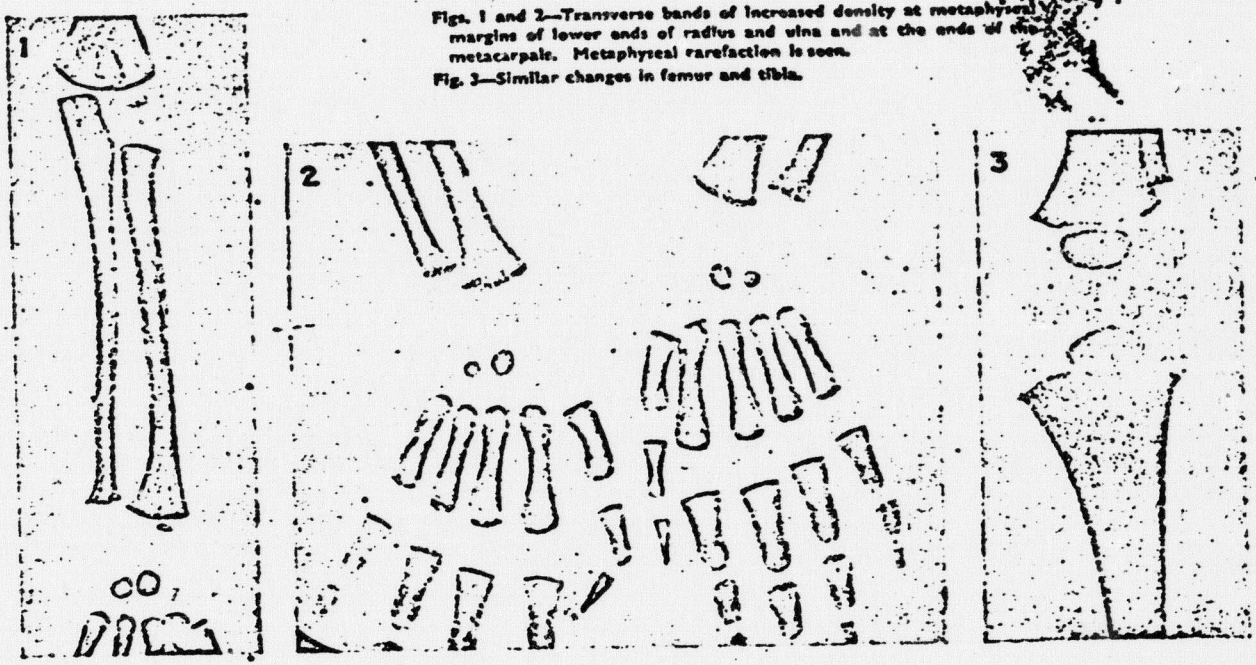
a diminutive appearance, sunken eyes, and a slender neck, has sometimes suggested the diagnosis.

Clinical evidence of dehydration was relatively uncommon (6 cases) and was only seen where vomiting had been severe or long-continued. Though 8 infants were regarded as pale, anæmia was not a feature of the illness: haemoglobin values were commonly within normal limits for age and in only 4 cases were they below 75% (59%, 60%, 65%, and 70%). Only 1 infant was regarded as mentally retarded. Hypotonia—involving particularly the legs and sometimes extreme—was usual (14 cases). Other less constant findings were unexplained episodes of pyrexia (8 cases), faecal masses in the colon (6 cases), soft apical systolic murmurs (3 cases), and hypertension (2 cases out of 13 in which blood-pressure readings were made). Intercurrent infections (colds, bronchitis, tonsillitis, otitis) were seen in 6 cases. After periods ranging from one to twenty-two months (see table), vomiting finally stopped, appetite slowly improved, constipation lessened or disappeared and the infants began to gain weight and strength.

## THE BIOCHEMICAL PICTURE

In all but 2 cases the initial examination of the serum showed a calcium level above 12 mg. per 100 ml., and in some cases it was as high as 16–17 mg. The blood-urea level was almost always raised, the mean being 54 mg. per 100 ml. The highest values obtained for calcium and urea in each case are shown in the table. It should be noted that some of these values were probably in part attributable to dehydration, as shown by rises in the specific gravity of the plasma. Inorganic-phosphorus levels were within the normal range for children of this age, the mean value being 5·6 mg. per 100 ml. Values for sodium, chloride, and potassium were normal. The alkali reserve was generally within normal limits, but occasionally a little high. Estimation of plasma-proteins by salt fractionation gave normal readings (with an occasional high total value) the albumin:globulin ratio being normal. Electrophoresis on paper (13 cases) showed in 7 cases an increase in the $\alpha_2$-globulin at the expense of the $\beta$-globulin: in 2 cases the $\gamma$-globulin was also increased. Alkaline phosphatase occasionally showed a slight rise, and in 3 children the serum-cholesterol was raised. Serum-magnesium (7 cases) was within normal limits of 1–3 mg. per 100 ml. The changes in the serum-calcium and blood-urea during the illness are illustrated in the chart of a typical case (fig. 4). The raised calcium, paralleled by a raised urea, characterises the active stage of the condition; reversion to rather high normal values takes place after clinical recovery. In some cases the blood-urea showed a much slower return to normal.

*The urine* was examined in 15 cases. The reaction was varied: only 1 infant passed a persistently alkaline urine. Proteinuria was not a feature, and on microscopy a few pus cells were seen. 1 infant, however, had a pyuria with a heavy growth of *Staphylococcus aureus* and proteus. Scanty growth of *Escherichia coli* was found in



Figs. 1 and 2—Transverse bands of increased density at metaphyseal margins of lower ends of radius and ulna and at the ends of the metacarpals. Metaphyseal rarefaction is seen.

Fig. 3—Similar changes in femur and tibia.

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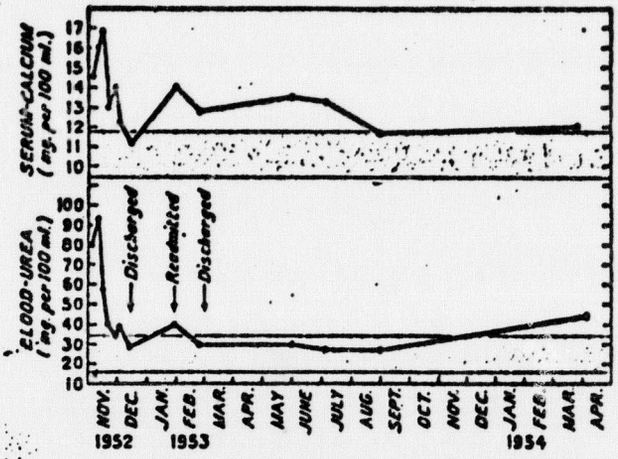


Fig. 4—Serum-calcium and blood-urea levels during treatment and follow-up.

6 cases and scanty proteus in 4; in 4 cases the urine was sterile. In 7 cases chromatography of the urine was normal; 1 case showed excretion of phenylalanine in unusual quantity, and 1 of proline.

### OTHER INVESTIGATIONS

On radiography, calcification in the kidneys was not detected in any case. As excess of intestinal gas commonly obscured the renal tracts, straight radiography and pyelography (2 cases) gave unsatisfactory results. The density of the skull, pelvis, vertebræ, and thoracic cage always appeared to be within normal limits. Radiographs of the wrists were taken in 15 cases: these were normal in 3 cases but 12 showed transverse bands of increased density at the metaphyseal margins of the lower ends of the radius and ulna with a similar appearance in the metacarpals in some cases (figs. 1 and 2). In 8 cases a similar appearance was noted in the femur and tibia (fig. 3). These bands were single, narrow, and well defined, quite unlike "growth lines" (which were present in addition in 4 cases); they were reminiscent of the dense lines seen in lead poisoning. In 1 child the bands were seen to develop as the illness progressed. In 4 children followed to recovery, the bands have disappeared. In 7 cases an additional feature has been a zone of slight rarefaction in the metaphysis, proximal to which the normal density of the diaphysis has been resumed.

Electro-encephalography (3 cases) and electrocardiography (2) showed nothing abnormal.

### THE DIAGNOSIS

In the absence of any of the common causes of wasting in infancy, a biochemical examination of the serum may be of value in suggesting the diagnosis. The pyuria of pyelonephritis is generally more severe than that of idiopathic hypercalcæmia, and the latter can be distin-

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guished from pink disease by the absence of irritability, photophobia, rashes, and tachycardia. But idiopathic renal acidosis cannot be satisfactorily diagnosed on clinical grounds alone.

A study of these 16 cases, and of 13 cases of renal acidosis occurring during the same period, displays certain points which may help in the differential diagnosis. The infants with renal acidosis had less often had vitamin D added to their feeds, and their illness had begun at a rather later age. The cardinal symptoms of anorexia, vomiting, constipation, and failure to thrive were common to both syndromes. Irritability and sighing respirations were additional but inconstant features of renal acidosis. Wasting was present in both groups of cases. Faecal masses, clinical dehydration, and unexplained pyrexia were more often seen in renal acidosis, whilst hypotonia, uncommon in renal acidosis, was characteristic of the hypercalcæmic syndrome. Urine containing a trace of protein, and alkaline or neutral in reaction, was characteristic of renal acidosis; in the hypercalcæmic cases the reaction was variable and proteinuria was absent. Minor pyuria was found in both. Radiological sclerosis of the metaphyseal margin, similar to that noted in idiopathic hypercalcæmia, has been observed in several cases of renal acidosis. The final distinction was made on the serum chemistry. The essential difference was the finding of a persistently lowered alkali reserve in the cases of renal acidosis. This acidæmia was not a feature of idiopathic hypercalcæmia, the alkali reserve being generally within normal limits or in some cases slightly raised.

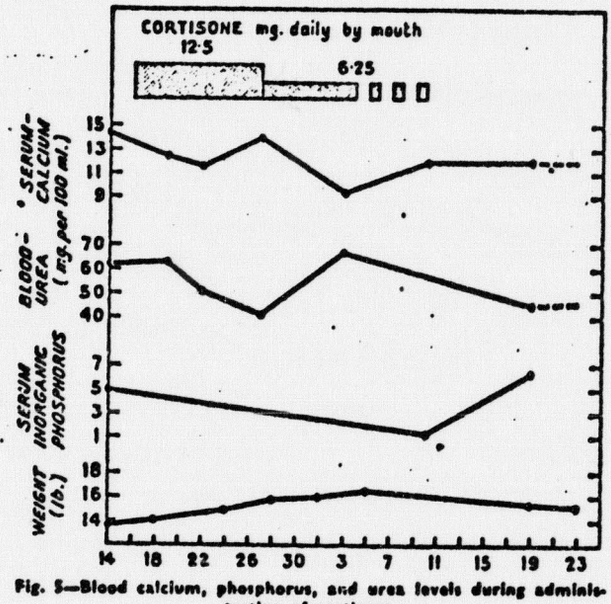


Fig. 3—Blood calcium, phosphorus, and urea levels during administration of cortisone.

A transient elevation of the serum-calcium was found in 9 of the 13 cases of renal acidosis. In 3 cases this was noted on the original biochemical examination but disappeared when alkali therapy commenced. In 1 case hypercalcæmia was found on the first examination and once again during the course of therapy. 2 other cases showed raised serum-calcium levels as isolated incidents during the course of treatment and while acidosis was still present. In 1 case the hypercalcæmia persisted after return of the alkali reserve to normal. In 2 cases a high serum-calcium was found on one occasion after apparent recovery from the renal acidosis. In all other respects these cases were typical of renal acidosis.

### TREATMENT

Of the 16 children, 14 were admitted to hospital and the other two were observed as outpatients. 13 received no treatment apart from symptomatic measures to relieve constipation and (when present) dehydration and infection. These infants were given their usual diets without vitamin-D supplements. So as to reduce the vitamin-D intake further, a change was usually made from vitamin-D-fortified milks to liquid cow's milk. In several cases a synthetic diet of low calcium content and free of vitamin D was given for short periods: it was composed of soya flour, liquid glucose, peanut oil, and arrowroot made up with water and contained about 75 mg. calcium per pint. In 2 of these cases, in which the periods of trial were probably too short, the results were inconclusive; but in 1 case this diet produced a gratifying response both clinically and chemically. In 1 infant a course of cortisone was given: the dose was 12·5 mg. daily by mouth, with gradual withdrawal: potassium chloride and oxytetracycline (terramycin) were given prophylactically, and a normal diet was continued. Clinical improvement was striking and the gain in weight was accelerated. The changes in the serum (fig. 5) comprised a fall in calcium, phosphorus, urea, and potassium levels with subsequent rise on cessation of therapy which was followed by a fall in weight. The fall in the phosphorus level was particularly marked. The urinary excretion of calcium was not estimated. It is possible that this child was already entering the recovery stage and that some of the changes were non-specific effects of cortisone. Nevertheless the biochemical response is of interest and merits further study. Similar findings were reported by Dent, Flynn, and Nabarro (1953) in cases of sarcoidosis with hypercalcæmia and impairment of renal function.

### FOLLOW-UP (SEE TABLE)

3 infants remain in the active stage of the disease and 1 has been lost sight of. 12 have been followed from apparent clinical recovery for varying periods. 4 of these have apparently regained their normal rate of growth and reached their expected height and weight, but 8 still remain below their expected stature. 4 of these 8 still show blood-urea levels at or slightly above the upper

limit of normal, in 1 case even after eighteen months. Urine at follow-up has shown minor pyuria (" occasional pus cell ") in 5 cases and scanty infecting organisms in 7. 1 infant had a florid *Esch. coli* urinary infection. 2 infants had become anæmic.

## Discussion

The clinical and chemical features of these cases are typical of the condition as described by Lightwood (1933a and b) and Payne (1932). In view of the known tendency to spontaneous recovery, and the lack of hypophosphatæmia, hyperparathyroidism appears an unlikely cause. It has been suggested (Creery 1953) that alkali medication might be a causal factor, but in the present series the syndrome has been seen to develop in the absence of such therapy. Similarly there is no direct evidence to implicate previous pyelonephritis as an ætiological agent, and the pyuria commonly found is probably secondary in nature (Lightwood 1952b).

Smith (1951) stated that ingestion of increasing amounts of calcium led to larger faecal losses but also to surprising degrees of increased retention, and that the degree of retention depended mostly on the amount of calcium in the infant's diet, which is 4–6 times as great with cow's milk as with human milk. Stearns (1939) observed that retention of calcium was much greater when vitamin D was added, especially if the diet was alkaline in ash; that infants fed with ample vitamin D tended to have serum-calcium levels at the upper limit of normal; and that the urinary excretion of calcium (which she said was normally under 20 mg. in twenty-four hours) was higher in those infants who were fed on cow's milk. It is known that increased calcium excretion through the kidneys may initiate tubular calcification (Albright and Reifenstein 1948, Dufault and Tobias 1954) and further that chronic hypercalcæmia may give rise to hyalinisation of the glomeruli (Dent, Flynn, and Nabarro 1953) with subsequent renal impairment and azotæmia.

Thatcher (1936), in his report of a case which presented a clinical picture similar to the syndrome under discussion, attributed the illness to vitamin-D intoxication, although the intake had not been markedly excessive by accepted standards. Variation of personal sensitiveness to vitamin D was suggested by Bicknell and Prescott (1942). Of interest in this connection is the observation of Jeans (1950) that vitamin D in a daily dosage of about 1800 I.U. may give rise to anorexia, loss of weight, and retardation of linear growth. He regarded these as mild manifestations of hypervitaminosis D during therapy of an order usually considered reasonable and harmless. He also pointed out that an additional feature of vitamin-D intoxication in infants was a dense deposition of mineral in the zone of provisional calcification in the metaphyses of long bones, this deposition being made at the expense of the diaphysis. Similar findings had previously been reported by Ross and Williams (1939), and further elaborated by Ross (1952), who noted in some cases a zone of rarefaction proximal to the dense line, and periosteal changes. Lightwood (1953), in

seeking an explanation for the hypercalcæmia, has put forward the hypothesis that there may be an abnormal sensitivity to vitamin D in these children. Unequivocal evidence of such a sensitivity is difficult to obtain, especially as it may be only temporary.

In one of our children in whom the serum-calcium had returned to normal without specific treatment and who was receiving a high calcium intake, the addition of 2000 I.U. vitamin D daily was accompanied by a rise in the serum-calcium from 11 mg. per 100 ml. to 12·4 mg.; in a period of two weeks the blood-urea rose from 30 mg. per 100 ml. to 46 mg. Yet on continuing the vitamin D for a further ten days the serum-calcium fell to 11·4 mg. and the blood-urea to 36·4 mg. Throughout these changes the child continued to improve clinically.

If, however, this postulate of abnormal sensitivity is correct, the radiological changes in the long bones of our cases, similar in nature to those described in hypervitaminosis D, are probably of significance.

In our series there is clear evidence for high calcium intake from early infancy. The low rate and short duration of breast-feeding is notable, and no example of the syndrome has so far been seen in a fully breast-fed infant. Evidence for hypercalciuria is less definite. Reliable figures for twenty-four-hour urinary excretion of calcium were obtained in 7 cases, the figures being 67·1, 54, 48·2, 40, 50·5, 60·7 and 47·75 mg.; but none was obtained in the early stages of the disease. If one accepts Stearns's figure of 20 mg. as normal, these figures probably represent increased levels of urinary calcium. On the other hand Knapp (1947) gave normal figures of 1–82 mg. daily for infants under six months old fed on cow's milk and added vitamin D; so there seems to be considerable variation from infant to infant. In all but 2 of our cases vitamin-D intake had been more than adequate by accepted standards, and in 3 cases it was over 2000 I.U. daily. Calcium and vitamin-D intakes of this order make it probable that there was alimentary over-absorption of calcium, which could well be the basis of the syndrome. In artificially fed infants, 30–50% of ingested calcium is said to be retained (Eliot and Park 1950). Several four-day calcium balance experiments in this series have had to be abandoned or the results discarded because of vomiting, and satisfactory balances have been carried out on 3 infants. 2, fed on diets high in calcium (such as they were accustomed to receive before admission) and without added vitamin D, showed retention of 57% and 56·7%. A further infant, fed on vitamin-D-fortified milk with a high total calcium-content had a retention of 41·5%. These experiments, again, were not made in the early stages of the disease. We think that they indicate retention of calcium at the upper limit of normal.

If hypercalcæmia can be caused by such overabsorption, most if not all of the other findings can be satisfactorily explained. Anorexia, vomiting, constipation, muscular weakness, and hypotonicity are all probably related in some part to the hypercalcæmia per se. Loss of weight and failure of linear growth could result from

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insufficient nutrition. Impairment of renal function will follow hypercalcæmia and hypercalciuria if present. Tubular calcification may be sufficient to give rise to pyuria and may predispose to the mild urinary infection so commonly found. Polyuria and thirst are presumably of renal origin. Harris (1954) has pointed out that sulphadimidine can adversely influence renal function in these cases, and such therapy is rightly condemned. Changes in the plasma-proteins may be compensatory and directed towards the carriage of the increased serum-calcium. It is tempting to regard the electrophoretic evidence of an increased $\alpha_2$-globulin as analogous to the increase in the copper-carrying protein cæruloplasmin in hepatolenticular degeneration (Holmberg and Laurell 1947, 1948). Changes in γ-globulin concentration may be the result of intercurrent infection. The relatively minor changes which we have noted in the long bones of our cases seem likely to be related to interference with growth in combination with hypercalcæmia and increase in the "calcium-phosphorus product" (Creery 1953, Harris 1954). The hypercalcæmia sometimes found in idiopathic renal acidosis is at present unexplained; it may arise in a way similar to that suggested above, or it may be related to changes in the acid-base balance of the blood.

To prevent this condition it would seem that we must constantly encourage breast-feeding and discourage unnecessarily large doses of vitamin D especially when vitamin-fortified dried milks and foods are being used. A rational therapy should include a diet low in calcium and free from vitamin D, such as has recently been suggested by Ferguson and McGowan (1954). From our experience we cannot say definitely how long this treatment should be continued, but we think that it is of most value to tide the infant over the acute stage of the illness and should be followed by a gradual return to normal feeding without excessive milk and with no added vitamin D. The results of such treatment may perhaps be regarded with some scepticism in the light of the spontaneous recovery which can confidently be anticipated.

The immediate prognosis is good, and all our infants have so far survived. A long follow-up will be needed to determine whether renal function remains unimpaired in those cases in which the blood-urea is still raised, and to see whether normal stature is always attained.

## Summary

The clinical, chemical, and radiological features of 16 cases of idiopathic hypercalcæmia of infants, with failure to thrive, are described.

The only constant ætiological factor is a high calcium intake from early infancy, usually associated with a more than adequate amount of vitamin D in the diet.

The possible mechanism of production of the syndrome, based on alimentary over-absorption of calcium, is discussed. The prophylaxis, treatment, and prognosis are outlined.

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# IDIOPATHIC HYPERCALCAEMIA IN AN INFANT

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## CLINICAL AND POST-MORTEM FINDINGS IN ONE CASE

BY

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(RECEIVED FOR PUBLICATION JUNE 11, 1954)

Idiopathic hypercalcaemic syndromes in infancy are now well recognized clinically (Lightwood, 1952a and b; Payne, 1952; Fanconi, Girardet, Schlesinger, Butler and Black, 1952; Creery, 1953; Lightwood and Stapleton, 1953; Lowe, Henderson, Park and McGreal, 1954; Creery and Neill, 1954, and *The Lancet*, leading article July 17, 1954). They are, in our opinion, separate from infantile renal acidosis, and Lightwood and Stapleton divide them into two groups. The classification is accepted by Lowe *et al.* In one group the course is transient and benign. There are no significant bony changes, no cardiac murmurs and probably no hypertension. On recovery the inteligence is normal. In the second group the course is prolonged and severe. There are bony changes resembling osteopetrosis, a loud systolic bruit, hypertension, often hypercholesterolaemia, a characteristic facies and impaired mental development. In the papers mentioned above there is one recorded histological report of a renal biopsy in a case which had run a prolonged and severe course (Lowe *et al.*). In a preliminary communication concerning a similar case (Dawson and Craig, 1954) we had previously tentatively suggested a primary renal origin for the condition. This view has had to be modified as a result of further study. Because necropsy and histological reports on these conditions are rare we think it worth while to present the findings in a single case.

### Case Report

Paul D., a boy, was the first child of healthy, unrelated parents. A maternal cousin of the mother had a deformity of the feet. Otherwise there were no known developmental anomalies in the family. Delivery was normal and birth weight 5 lb. 14 oz. Progress in the early months was satisfactory although it was noted that from the age of 3 weeks the baby was unusually quiet, inclined to sleep too much and rather unresponsive to attention. He was first referred to hospital when 23 weeks old on account of anorexia and persistent vomiting for three weeks. On examination the infant was unable to hold his head up. There was generalized hypotonia, gross plagiocephaly and asymmetry of the face and thorax, right calcaneovalgus, a large umbilical hernia, hypertension and a loud systolic murmur audible over the entire chest (Fig. 1). The cardiac murmur had not been present when the baby was thoroughly examined on two occasions during the neonatal period.

FIG. 1.—Paul D., aged 37 weeks. Note the facial and cranial asymmetry.

His weight showed an irregular but progressive decline. Unexplained periods of pyrexia occurred at irregular intervals and the child died unexpectedly during one of them at the age of 47 weeks. Apathy and listlessness, lack of emotional response, reluctance to feed and constipation were constant features in hospital. The abnormal behaviour pattern suggested that mental progress might be impaired. Dogmatic conclusions were not justified, however, in view of the child's age, of the associated physical weakness, and of the fact that impaired hearing was suspected by several independent observers.

The baby was fed wholly at the breast until the age of 3 months when a change was made to a full cream dried cow's milk preparation, and when for the first time concentrated orange juice (1 teaspoonful) and pure cod liver oil (5 drops) were given daily. Medicaments given to the child consisted of six teething powders (each containing ¼ grain of calomel) in the sixth month of life; and from the age of 13 to 23 weeks milk of magnesia (½ teaspoonful) on alternate days, and 2 grains of soda

TABLE I

BLOOD SERUM BIOCHEMISTRY (mg./100 ml.)

| Date | Sodium | Potassium | Total Calcium | Ionized | Iron | Phosphorus | Chloride | Bicarb. | Urea Nitrogen | $CO_2$ | Cholesterol | Total Proteins | Albumin | Globulin | A/G Ratio |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 17.8.53 | 300 | | | | | | | | | | | | | | |
| 24.8.53 | | | | | | | | | | | | | | | |
| 28.8.53 | | | 16·0 | | | | | | 28·6 | | 250 | | | | |
| 31.8.53 | 310 | 14 | 13·7 | | | | | | 27·6 | | 300 | 6·9 | | | |
| 12.9.53 | | | 16·0 | | 9·1a | | | | 26·6 | 60 | | 6·7 | 4·8 | 3·2 | 2·1 |
| 17.9.53 | 320 | 25·9 | | | 3·6 | | | | 47·6 | | | | | | |
| 29.9.53 | | | 14·1 | | 9·4 | | | 102 | 51·6 | | 315 | | | | |
| 21.10.53 | | | 16·4 | | | | | 110 | | | 310 | | | | |
| 28.10.53 | | | | | | | | 88 | | | 349 | 8·8 | 3·7 | 4·8 | 0·8:1 |
| 3.11.53 | | | | | | | | | 30·1 | | | | | | |
| 10.11.53 | | | | | | | | | 23·7 | | | | | | |
| 2.12.53 | 345 | 17·5 | | | 5·4 | | | | 24·5 | | | | | | |
| 15.12.53 | | | | | | | | | | 53 | 330 | 7·4 | | | |
| | | | | | | | | | | 55 | | 7·1 | | | |

TABLE 2

URINARY FINDINGS

| Date | |
|---|---|
| 31.8.53 | Pus cells, numer... Predominant g... C.s occasion... ...rous. |
| 7.9.53 | Polymorphon... ...some red cell... ...cytes, moderate number, ...nal hyaline casts. *Proteus*. Albumin, trace, pH ... Calcium, 12·9 mg. per 100 ml. |
| 14.9.53 | Pus cells, moderate number, many cellular casts, granular casts, moderate number. *Proteus*, profuse growth, occasional colony of staphylococcus. Albumin, trace, pH 7·0 |
| 29.9.53 | Many polymorphs and some red and epithelial cells. Moderate growth of *Proteus*, light growth of staphylococcus, sensitive to chloromycetin. Albumin, trace, pH 6·3. Calcium 12·8 mg. |
| 26.10.53 | Occasional polymorph and red cells. Very occasional granular casts. Heavy growth of *Proteus* and a Gram-positive coccus. Albumin, trace, pH 6·4 |
| 10.11.53 | Nil. Scanty growth of coliform organism of doubtful significance. pH 6·3, albumin, trace, calcium, 12·9 mg. |
| 17.11.53 | Occasional leucocyte and red cell. Moderate growth of *Ps. procyanea* and a coliform organism. |
| 3.12.53 | Desquamated epithelial cells and an occasional pus cell. Mixed growth *Proteus* and staphylococcus. Albumin, trace, pH 6·4 |

[a] Frequent use was made of Sulkowitch's reagent but on no occasion did the results suggest excessive calcium excretion.
Chromatography established the absence of reducing substances and of any abnormal amino-aciduria.
Urea clearance was 21% (second hour).

TABLE 3

MISCELLANEOUS FINDINGS

| Date | Age (weeks) | Investigation | Results and Conclusion |
|---|---|---|---|
| 25.9.53 | 35 | Fractional test meal | Acid secretion within normal limits |
| 12.9.53 | 34 | Wassermann | Negative |
| 28.8.53 | 31 | Electrocardiograph | Elevation of ST segment in leads 2, 3, V4 and V6. T waves prominent |
| 12.11.53 | 42 | " " | |
| 17.7.53 | 25 | *Radiological* Skull and wrist | Fontanelle open. Convolutional markings posterior part of skull. Three small centres of ossification in wrist |
| 26.8.53 | 31 | Skeleton | No detectable abnormality in bone structure |
| 30.9.53 | 36 | Skull. Long bones. Abdomen | Bands of increased density at ends of long bones particularly at distal metaphyses of radius and ulna. Peripheral density to ossification centres of tarsal bones and at knee joints. No evidence of renal calcification |
| 6.11.53 | 41 | Skull. Long bone | Skull, basal sclerosis and asymmetry but no abnormality of sutures. Long bone, continued deposit of sclerotic bone metaphyses. Two ossific nuclei in each wrist. Epiphyses of femoral heads well developed. Epiphyses and tarsal bone—central core of bone of normal intensity with existing sclerotic changes situated peripherally. Skeletal development not delayed |

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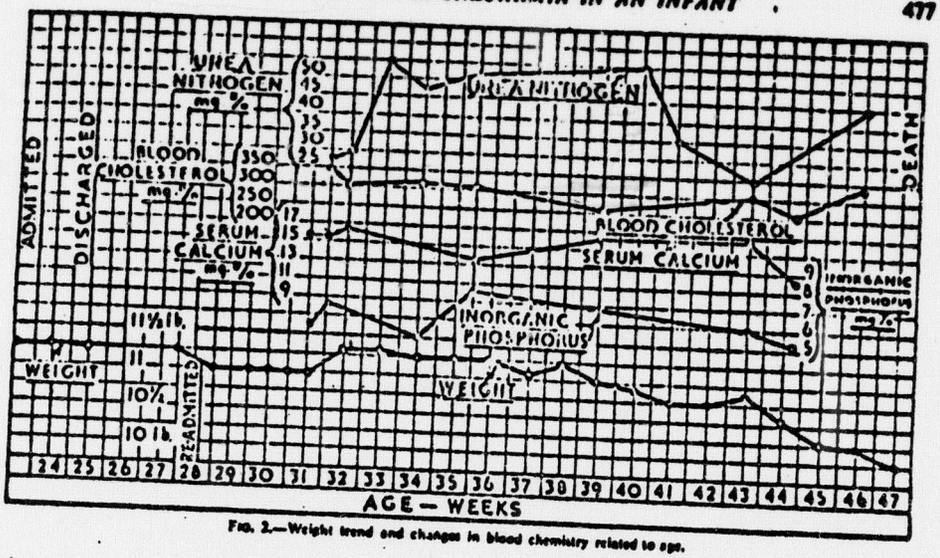


FIG. 2.—Weight trend and changes in blood chemistry related to age.

bicarbonate (in a proprietary mixture) daily. The infant was never given sulphonamides.

INVESTIGATIONS. The results of investigations are detailed in Tables 1-3 and Fig. 2. There were persistently raised serum calcium, blood cholesterol and urea nitrogen levels. Renal function was impaired, but there was no evidence of renal acidosis or of parathyroid hyperactivity. Radiologically there was moderately increased density in certain bones (Fig. 3) but no nephrocalcinosis. Blood cultures at the ages of 27, 44 and 47 weeks were all sterile, and blood counts between July 11 and November 26 gave: Hb 64-79%, R.B.C.s 3·4-4·2 m., W.B.C.s 7,600-20,400 per c.mm. Numerous blood pressure readings were recorded during the last six months of life. Systolic readings were always in the neighbourhood of 140 to 150 mm. Hg and the diastolic readings between 50 and 60 mm. Hg.

FIG. 3.—Radiograph of the skull at 46 weeks, showing excessive deposit of sclerotic bone at the base of the skull.

The mother of Paul D. has since given birth to a second baby whose progress has been uninterrupted and who at 9 months of age is in every way healthy. The results of examination of the mother's blood one month before delivery of her second baby are summarized in Table 4.

TABLE 4

RESULTS OF EXAMINATION OF THE MOTHER'S BLOOD

| Serum (mg./100 ml.) | |
|---|---|
| Calcium | 9·1 |
| Inorganic phosphate | 3·1 |
| Alkaline phosphatase | 13·1 |
| Cholesterol | 203 |
| Urea | 18 |
| Total protein | 5·6 |
| A/G ratio | 2·8 : 1 |

## Necropsy

Necropsy was performed 18 hours after death. The body was that of a wasted male child, weight 5·0 kg. (10 lb. 4 oz.) and height 63 cm. (25¼ in.). The upper and lower incisor teeth had erupted. The facial and thoracic asymmetry were not so noticeable as in life.

**Cardiovascular System.** The heart weighed 55 g. (expected weight 30-40 g.), and there was moderate left ventricular hypertrophy. The remaining chambers and all valves were normal. The foramen ovale and the ductus arteriosus were closed. The coronary arteries and myocardium were normal on section, as was the pericardium. No atheroma or calcification was seen in the aorta.

**Respiratory System.** There was no infection of the middle ears or tonsils. The trachea and main bronchi were normal. There was patchy bronchopneumonic consolidation of both lower lobes, with moderate congestion of the rest of the lungs, but no evidence of calcification.

**Alimentary System.** The mouth, pharynx, oesophagus, stomach and small intestine were normal. There were hard, constipated faeces in the transverse, descending and pelvic colon.

The liver (250 g.) was soft and rather pale, and the cut surface suggested fatty change. The gall-bladder was normal, and the bile and cystic ducts were patent. The spleen (16 g.) and pancreas were normal.

**Urogenital System.** The kidneys together weighed 35 g., and the capsules of both stripped easily leaving a smooth surface. No grittiness was felt on section, and there were no visible calcium deposits. The cortex and medulla both presented a normal appearance. The renal pelves, ureters, bladder, urethra and prostate were normal.

The left testis was in the scrotum and the right testis in the inguinal canal.

**Endocrine System.** The neck organs were removed en bloc and fixed, and a careful dissection was subsequently made in a search for parathyroid glands. Some 20 small pieces of tissue from this region were sectioned, but only two small pieces of parathyroid tissue were found. No other parathyroid tissue could be identified. The thyroid and suprarenal glands were normal.

**Central Nervous System.** The brain, spinal cord, and meninges all appeared normal.

**Skeletal System.** The base of the skull did not appear thickened to the naked eye, and the lower jaw, which was removed, appeared normal. The shaft of the right femur showed definite thickening of the dense cortical bone. No other abnormalities were seen in the other bones examined.

### Histology

**Material and Methods.** Material was taken from the heart, aorta, tonsil, lung, stomach, intestine, liver, pancreas, spleen, kidney, testis, suprarenal, thyroid, parathyroid, thymus, pituitary, brain, spinal cord, upper and lower jaw, base of skull, femur, ribs and voluntary muscle. It was fixed in 10% formol saline. Blocks of kidney were also fixed in cold acetone and embedded in low melting point wax for phosphatase estimations. Bone was decalcified in 20% formic acid.

Ehrlich's haematoxylin and eosin were used for routine staining, and in addition alizarin red, purpurin and xanthopurpurin stains, Von Kossa's method, and the gallamine method of Steck (1949) for calcium; ferri- and ferro-cyanide methods for iron; the azo-dye coupling method of Pearse (1953) using the salt of 4 chloro-o-dianisidine for alkaline phosphatase; and the periodic-acid-Schiff stain, picro Mallory stain, and elastin stain of Weigert for general renal pathology. Sudan IV and Sudan black B were used as fat stains on frozen sections.

The thyroid gland was serially blocked in a further unsuccessful search for parathyroid tissue.

**Kidney.** Glomeruli are present in normal numbers, and about 90% are normal histologically. In the remaining 10% the principal abnormality is the deposition of hyaline material in glomerular tufts, in some situations diffusely throughout the tuft, and in others localized to one or more lobules (Fig. 4). Certain tufts have been almost completely replaced by hyaline material. Although some hyaline change may normally be seen in kidneys at this age, these findings were considered to be excessive. Occasional epithelial crescents derived from the parietal layer of Bowman's capsule are present (Fig. 5). There is no glomerular calcification.

While some convoluted tubules are normal, others show severe changes, and it is not always possible to differentiate proximal from distal tubules. Vacuolation of proximal tubule cells results in partial or complete occlusion of the lumen in places (Fig. 6). The vacuoles failed to stain with fat stains, with the periodic-acid-Schiff (P.A.S.) method, or with any of the methods for calcium. The distal and collecting tubules contain eosinophilic hyaline casts, which stain red with P.A.S., and basophilic material, which stains positively with the gallamine stain for calcium (Fig. 7) but does not give a positive stain for iron. In certain situations the epithelium of the tubules is destroyed, while in others a layer of regenerating epithelium extends over the hyaline casts (Fig. 8). Calcified material has been extruded into the interstitial tissues of the cortex from the distal tubules (Figs. 9 and 10). A fibrous reaction has been stimulated in these situations, and in the medullary (but not in the cortical) tissues is associated with occasional giant cells. There are no chronic inflammatory cells. The loops of Henle are compressed by a moderate interstitial fibrosis, but are not otherwise greatly altered. A few small collections of lymphocytes are found beneath the renal capsule. There are no inflammatory changes in the renal pelvis. Renal arteries and arterioles are normal. Sections stained for alkaline phosphatase show no constant relationship between sites of phosphatase activity and calcium deposition.

The calcified material in the tubules stains best with gallamine; staining with von Kossa's method is inconstant, and stains for iron are also negative. On the other hand material which has been deposited in the interstitial tissues of cortex or medulla stains readily with

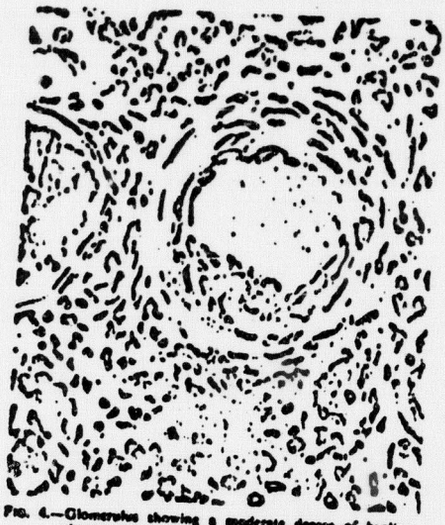

FIG. 4.—Glomerulus showing a moderate degree of hyaline change. (Haematoxylin and eosin. × 300.)

FIG. 5.—Glomerulus showing epithelial crescent. (Haematoxylin and eosin. × 300.)

FIG. 6.—Proximal convoluted tubule showing vacuolation of the tubular cells. (Haematoxylin and eosin. × 300.)

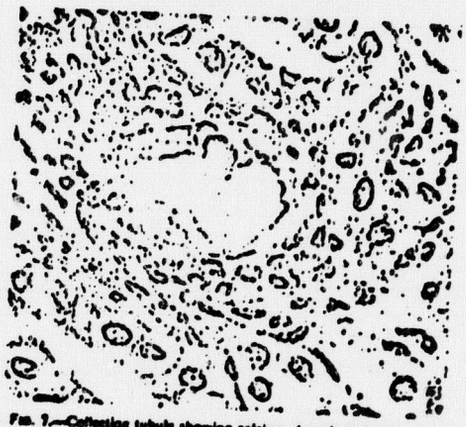

FIG. 7.—Collecting tubule showing calcium deposit in lumen of tubule. (Stoch's gallamine method. × 300.)

gallamine and with ferri- and ferro-cyanide methods for iron (Fig. 11). At no time could any positive staining be obtained with purpurin, xanthopurpurin or alizarin red (Cameron, 1930).

**Lungs.** There is an organizing pneumonic process around fat droplets, which are almost certainly inhaled milk. There is no calcification present in any of the sections examined.

**Skeletal Tissues.** Femoral and tibial epiphyses and costal cartilages are normal. The shaft of the femur shows a moderate increase in bony thickness when compared with an infant of the same age group, but the

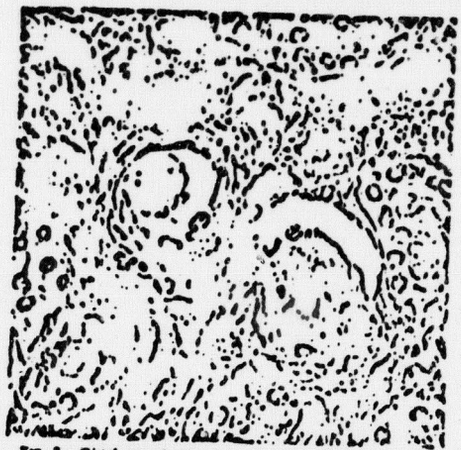

FIG. 8.—Distal convoluted tubule showing re-epithelisation of hyaline cast. (Haematoxylin and eosin. × 500.)

FIG. 9.—Collecting tubule showing calcium deposit becoming extruded from lumen. (Stoeltzner's gallamine method. × 500.)

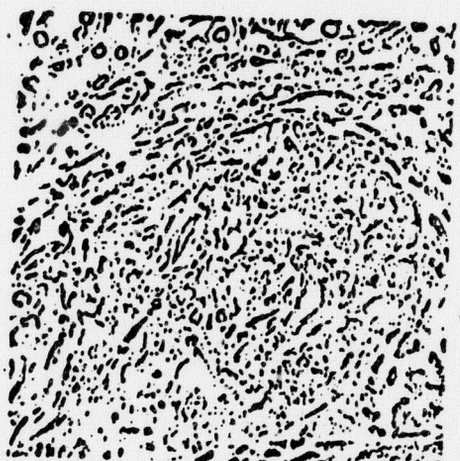

FIG. 10.—Medulla showing calcium deposits with fibrous tissue reaction in interstitial tissue. (Haematoxylin and eosin. × 380.)

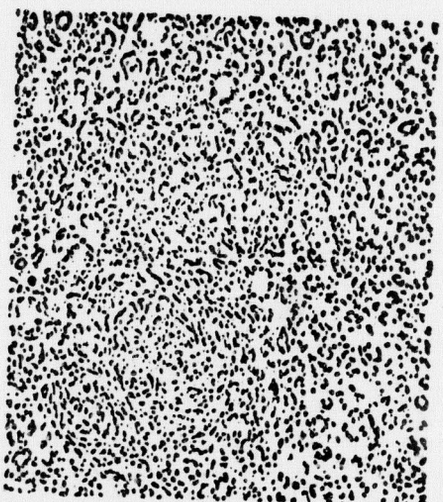

FIG. 11.—A general view of the medulla to show diffuse deposits of calcium with fibrosis. (Haematoxylin and eosin. × 60.)

bone structure is normal. Sections from the base of the skull suggest some thickening but again show normal bone structure.

Sections of the jaws and teeth show normal development and normal calcification of deciduous molars. An unusual and abnormal feature is calcified areas in the pulp of the lower central incisors (Figs. 12 and 13).

**Endocrine Glands.** The two small pieces of parathyroid tissue show a completely normal structure. The pituitary has not been serially sectioned but there is no indication of a disturbance in the customary ratio of chromophil to chromophobe or acidophil to basophil cells in the sections examined.

The remaining tissues examined are normal. There

is no evidence in the stomach or elsewhere of metastatic calcification.

FIG. 12.—Radiograph of the lower jaw showing calcium deposits in pulp of the incisor teeth.

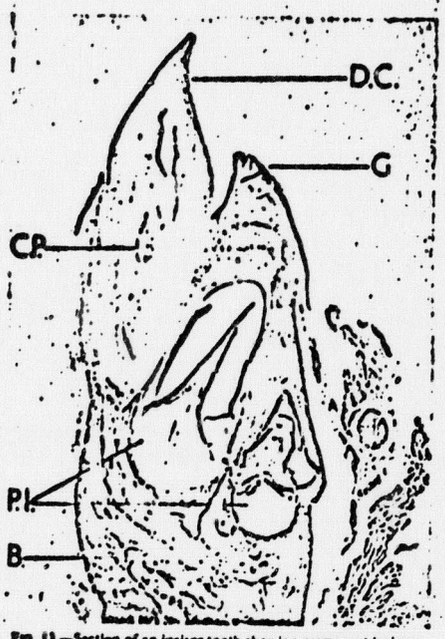


FIG. 13.—Section of an incisor tooth showing permanent incisors (P.I.), gum margin (G.), and abnormal calcium deposit (C.P.) in the pulp of deciduous incisor. (Haematoxylin and eosin. × 6.)

### Discussion

Butler, Wilson and Farber (1936) described renal lesions in children with hypercalcaemia and acidosis. They saw calcium deposits between the basement membrane and epithelial cells of collecting tubules, a few deposits in proximal tubules, degeneration of tubular epithelium and calcified deposits surrounded by fibrosis and giant cell infiltration around affected tubules. Their cases appear to belong clinically to the renal acidosis group or possibly to the transient and benign group of idiopathic hypercalcaemia which may sometimes show acidosis. Govan (1950) described hyalinized glomeruli, vacuolation of proximal tubular epithelium, calcified casts in distal and collecting tubules, and deposits of calcium associated with fibrosis in the surrounding tissues in a case of renal acidosis in a girl of 29; death may have been complicated by sensitivity to sulphonamides. The histology of both of these cases is not dissimilar to our own, though there are no calcium deposits between basement membranes and epithelium in our case. Govan attributed the vacuolation of proximal tubules to possible phosphorus absorption, and we were at first inclined to think of the tubular vacuolation in our case as primary, representing a nephron nephrosis of the type seen in sulphonamide or mercury poisoning. The fact that Albright, Consolazio, Coombs, Sulkowitch and Talbott (1940) and Albright, Burnett, Parson, Reifenstein and Roos (1946) postulated a primary tubule defect in infantile renal acidosis, often associated with hypercalcaemia, seemed to support this possibility. Further study has changed this view.

Large amounts of calcium-containing material in distal and collecting tubules justifies acceptance of the view that calcium precipitates out as the filtrate becomes concentrated, and that the interstitial fibrosis and probably the tubular epithelial degeneration are secondary to the extrusion of calcium into surrounding tissues. The positive staining for iron as well as calcium in extratubular but not intratubular material supports this view (Cameron, 1952). Vacuolation of proximal tubules need not be primary, but occurs under appropriate osmotic conditions (Allen, 1951) which may well obtain here. Hyaline glomerular changes, besides occurring normally in infancy, have been described as secondary to hypercalcaemia (Dent, Flynn and Nabarro, 1953). In the case of Paul D. no cause for a primary nephron nephrosis was found. On balance it is considered that the renal changes are to be regarded as secondary manifestations of hypercalcaemia, a view which would explain the similarity of lesions in renal acidosis and a severe and prolonged hypercalcaemia

which are clinically, radiologically and biochemically distinct.

Lowe *et al.* (1954) describe the results of renal biopsy in a child presenting clinical features similar to Paul D. Their findings resemble those in our case in the nature of the cortical and medullary changes, but differ in the presence of a granulomatous reaction around calcium deposits in the medulla as opposed to the cortex and in the presence of many abnormal glomeruli. It cannot be claimed that histological studies have as yet provided conclusive positive evidence concerning the aetiology of idiopathic hypercalcaemia in infancy. Increased alimentary absorption of calcium must be accepted as a possible explanation. If this be the explanation the facts concerning our case lend no support to the view that sensitivity to vitamin D may have been a contributory factor. Excessive intake of alkalis has been suggested as having a bearing on aetiology. The child, the subject of this paper, did receive alkalis in considerable amounts but not until symptoms had already become established. Alkalis may have had an aggravating effect but cannot be regarded as having any aetiological significance. Abnormal histological changes in bone and metastatic calcification were found in a case resembling that of Paul D. in other respects (Baar, 1954). The absence of such findings in the present case cannot be explained.

## Summary

A case of idiopathic hypercalcaemia of a severe and profonged type in a boy was studied clinically and at necropsy.

Clinical and biochemical findings included failure to thrive, lassitude, generalized hypotonia, irregular pyrexia, hypertension with a pronounced cardiac murmur, cranio-facial asymmetry and excessive irregular deposition of bone. Serum calcium, blood cholesterol and blood urea levels were raised, and there was evidence of renal impairment.

Histological findings in the kidneys included deposition of calcium in and around distal and collecting tubules, vacuolation of proximal tubule cells and hyaline glomerular changes. Abnormal histological changes in the bones were not seen. There was no evidence of metastatic calcification. An unexplained feature was calcium deposits in the pulp of certain incisor teeth. The parathyroid glands were normal.

Renal changes are regarded as secondary to hypercalcaemia, which it is suggested may have resulted from excessive absorption of calcium by the alimentary tract.

We are grateful to Professor F. S. Fowweather, Professor R. A. Willis, and Dr. W. Goldie of Leeds, and Dr. W. W. Payne of London, for help and advice; to the nursing staff of Princess Mary Ward, Leeds General Infirmary, for their cooperation in clinical observations; to Mr. W. H. Lawson for the photomicrographs, and to Mr. D. F. High for technical assistance.

We are particularly indebted to Professor T. T. Read of the School of Dentistry, Leeds, for his advice and opinions and also for Figs. 12 and 13.

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WOMAN'S AUXILIARY 62A

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# Vitamin D Intoxication

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THE toxicity of vitamin D, if given in sufficient dosage for a long enough period of time, is well documented.[1,2,3] It is regrettable that this danger is not universally appreciated by physicians and that it is almost unknown to the laity. Nevertheless, the lay public is able to obtain products containing large amounts of vitamin D on request. Vitamin D, in conjunction with calcium, has been advised for various arthritides in medical literature in the past[4] and even more currently in syndicated health columns.

A 67 year old white man was admitted to the hospital on February 12, 1956, for left inguinal herniorrhaphy. Routine admission laboratory studies revealed a hemoglobin of 9.1 grams per cent and erythrocytes, 3,500,000. Urinalysis was negative.

He had been treated for duodenal ulcer in 1916. Symptoms disappeared and he had little or no trouble with gastrointestinal symptoms afterward until May, 1952. Then epigastric distress recurred and bothered him frequently. He took large quantities of milk and aluminum hydroxide gel. On November 11, 1952, subtotal gastric resection was performed for massive gastrointestinal hemorrhage. A large benign gastric ulcer was found on the lesser curvature.

A right inguinal herniorrhaphy was performed on January 19, 1951. Shortly after this he complained of joint pains involving wrists, fingers, and shoulders. A diagnosis of rheumatoid arthritis was made and he was treated with ACTH. The early response was good. Therapy was changed to cortisone but this was discontinued after a few weeks "because of glycosuria."

From 1951, until this admission his joint complaints had been variable but almost constant and deformity had been progressive. The feet and ankles became involved. During 1950, firm and non-tender nodules, measuring from 0.5 to 2.0 centimeters appeared over the extensor surfaces of the toes, fingers, elbows, wrists, and Achilles' tendons. A few of the nodules had drained spontaneously, discharging a thick milky material. Aside from the joint abnormalities physical examination was within normal limits. The hemoglobin measured 9.1 grams per cent; erythrocytes were 3,500,000; white cell count, 8,000 with a normal differential. Blood urea nitrogen was 9.1 milligrams per cent and uric acid 4.06 milligrams per cent. The stools were negative for occult blood and complete gastrointestinal X-ray studies were negative. After one month on ferrous sulfate therapy, hemoglobin increased to 11.0 grams per cent and erythrocytes to 4,480,000. The stools were negative for occult blood. A left inguinal herniorrhaphy was performed and followed by an uneventful recovery.

On June 6, 1956, the patient was readmitted on the urologic service in a semi-stuporous state.

his wife said he had been bothered by urinary frequency and nocturia for two years and that for the past three months there had been a gradual increase in lethargy. More recently he appeared confused. During the few days prior to admission he slept for long periods. The urologist found no evidence of urinary tract disorder and the patient was transferred to the medical service.

Except for moderate pallor, the nodules on the extremities were the only remarkable physical abnormalities. Neurological examination revealed nothing unusual. The blood pressure was 110/70. Temperature was 98.4 degrees; pulse, 80. Initial and subsequent laboratory values are presented in Table 1. An electrocardiogram taken on February 3, 1956, showed sinus tachycardia with a rate of 110; otherwise the tracing was within normal limits. The Q-T segment measured 0.31 seconds. An electrocardiogram of June 15, 1956, showed a sinus rhythm of 90, Q-T segment 0.28 seconds, low voltage of all QRS segments and low T-1. On June 16, 1956, the quantitative 24 hour urinary excretion of calcium was 578.1 milligrams. Calcium intake had been limited to 150 milligrams daily.

Further exploration of the patient's history with his wife brought out that he had been taking vitamin D and calcium on the advice of an arthritic friend. She thought he had been using this medication for three months or longer. The intake of calcium consisted of one quart of milk and 12 grams of calcium lactate daily. The daily intake of vitamin D was 300,000 units. Roentgen examination of the chest and bones showed no abnormality other than scattered calcifications in the left upper abdominal quadrant. These calcifications were not in the kidney.

Treatment consisted of parenteral fluids, tube feedings of low calcium content, and whole blood transfusions to a total of 4,000 cc. Intake was patterned to the laboratory values and to the daily urine output, which varied from 1,200 to 1,800 cc. Over a period of two and one-half weeks the patient improved gradually; stupor was less conspicuous and he took a soft low calcium diet of approximately 1,500 calories. On June 26, 1956, the tip of the spleen was palpable for the first time. On July 1, 1956, he appeared more stuporous than he had been and the urine became dark brown. On July 2, 1956, he was jaundiced. He became comatose and more deeply jaundiced and on July 4, 1956, he expired. Permission for autopsy was refused.

## COMMENT

Failure to obtain autopsy permission prevents exclusion of primary hyperparathyroidism as a diagnostic possibility. The evidence supports a diagnosis of hypervitaminosis D. A past history of peptic ulcer and the existence over a period of time of moderate anemia are suggestive of primary hyperparathyroidism.

The absence of intestinal complaints after partial gastrectomy is not in accord with most reports on peptic ulcer surgery that is associated with hyperparathyroidism.[6] Gutman et al[6] first called attention to gastrointestinal symptoms in primary hyperparathyroidism. A later comprehensive study of hyperparathyroidism by Black[7] clarified the upper intestinal symptomatology of this condition. Black found clinical evidence of peptic ulcer in 24 per cent of patients with hyperparathyroidism and ulcer-like symptoms in 15 to 20 per cent more. In the patient reported here, the serum phosphorus and alkaline phosphatase values and the absence of skeletal changes[8,10] are of little help in differentiation. Phosphatase and skeletal changes would be unexpected in a patient of this sort with a high calcium intake.

Differentiation between hyperparathyroidism and the Burnett Milk-Alkali-Syndrome often difficult and even impossible clinically.[8,10] In this case Milk-Alkali-Syndrome is not a diagnostic problem because at no time was there a history of ingestion of large amounts of absorbable alkali. Furthermore, the marked acidosis and hypercalciuria eliminate it from further consideration.

The antirachitic effect of vitamin D was established by McCollum in 1922[4] when he separated this fraction from the vitamin A of cod liver oil. The same properties were found later in ultraviolet irradiated ergosterol. Subsequent purification resulted in vitamin $D^2$, or calciferol. If an adequate dietary intake of calcium and phosphorus is provided, vitamin D has a curative effect on rickets and osteomalacia, both of which develop as a failure of ossification of osteoid. Vitamin D exerts its influence by increasing the absorption of calcium from the upper intestinal tract. There is a resultant ab-

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TABLE 1

| Date | NA | K | Urine | | | | HGB. | RBC | HCT | WBC |
|---|---|---|---|---|---|---|---|---|---|---|
| | MEQ/L. | MEQ/L. | Sp. Gr. | Alb. | Sug. | Micro. | | | | |
| 6-6-56 | | | 1.010 | 0 | 0 | 8-12 hyal. casts | 7.9 | 2.01 | | 4,050 |
| 6-11-56 | | | | | | | 9.5 | | 28 | |
| 6-13-56 | | | | | | | 9.5 | | 28 | |
| 6-14-56 | | | | | | | | | | |
| 6-15-56 | | | | | | | | | | |
| 6-16-56 | | | | | | | | | 30 | |
| 6-17-56 | 131.7 | 4.74 | | | | | | | | |
| 6-18-56 | | | 1.010 | 0 | 0 | 30-40 WBC 40-50 RBC | | | | |
| 6-20-56 | | | | | | | | | 29 | |
| 6-23-56 | | | | | | | | | | |
| 6-24-56 | | | 1.010 | 0 | 0 | 10-12WBC 20-30RBC | | | | |
| 6-25-56 | | | | | | | | | | |
| 6-26-56 | | | | | | | | | 37 | |
| 6-27-56 | 130.4 | 4.7 | | | | | 11.0 | 3.81 | | 7,300 |
| 7-2-56 | | | 1.011 | + | 0 | 3-4 gram. bil. + 8-12WBC 8-16RBC Urob. 1:20+ | | | | |
| 7-3-56 | | | | | | | | | | |
| 7-4-56 | 132.6 | 4.3 | | | | | | | | |

sorption of phosphorus lower in the small intestine.[11] A lesser influence of vitamin D is that of increasing the renal excretion of phosphorus by decreasing its reabsorption in the tubules. A daily intake of 400 units of vitamin D is more than adequate in normal infants and adults.[6] The administration of vitamin D is followed by an early rise in the serum calcium and phosphorus. Later there is inhibition of the parathyroid glands, with a decrease in the renal phosphorus excretion. In a normal person on a diet limited to 150 milligrams of calcium in 24 hours there is an excretion of 100 to 200 milligrams in the urine in 24 hours and 300 to 400 milligrams in the stool. An increase in the dietary calcium is reflected mainly as increased excretion in the stool.

The degree of toxicity of vitamin D is variable. The shortest time reported is 12 days[12] at a dosage of 750,000 units a day. Most reports in the literature show an intake over a period of months or years. The toxicity of vitamin D is considerably increased in proportion to calcium intake. In the case presented here the period over which excessive doses of vitamin D are known to have been taken is shorter than most, but is quite sufficient for an advanced state of intoxication.

The admitting picture in this patient was considered as due to hypercalcemia of vitamin D intoxication. Chaplin et al.[13] have described these symptoms as weakness and fatigue with weight loss, nausea, vomiting, cramps, diarrhea, headache, paresthesias, vertigo, mental depression, urinary frequency, nocturia, and abnormal calcifications. Scharfman and Propp[14] stressed the importance of normocytic, normochromic anemia in these patients. They were of the opinion that the anemia is due to azotemia. This, however, is a matter of conjecture, particularly in view of the reported response of the anemia to iron therapy.[3] Extensive neoplastic metastases to bone is eliminated by virtue of their failure to appear on an X-ray survey.

The appearance of jaundice and the rapid downhill course in the past few days of this patient's life are open to question. Terminal fulminating hepatitis seems likely, although thrombosis of the portal and splenic veins deserves consideration.

Although adequate and repeated warnings of the danger of the ill advised use of vitamin D

TABLE I (Continued)

| | PBS | NPN | BUN | CO2 | CA | P | Alk. Phos. | Ser. Bil. | Ser. Prot. | Cryth. Flocc. | Cl. |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | MGM% | MGM% | MGM% | MEQ/L. | MGM% | MGM% | BU | MGM% | MGM% | | MEQ/L. |
| | 97 | 61.6 | | | | | | | | | |
| | | | 53.2 | 17 | 13.5 | 4.40 | 4.66 | | | | 100.2 |
| | | | | | | | | D .44<br>I .66<br>T1.00 | T6.59<br>A4.03<br>G2.56 | | |
| | | | 48.1 | | 15.06 | 4.4 | | | | | |
| | | | 64.2 | | 13.1 | 4.4 | | | | | |
| | | | 68.1 | | | | | | | | |
| | | | 64.5 | | 13.7 | 4.48 | | | | | |
| | | | | | | | | D13.3<br>I 1.4<br>T14.6 | | | |
| | | | 49 | 18.3 | 13.8 | 4 | | | | | |

have appeared in the literature for almost 30 years, this continues to be a real and probably not rare problem. It is wise to inquire in detail about the medications patients are taking. An innocuous history of taking "vitamin pills" may have considerable significance.

## SUMMARY

A fatal case is presented involving the ingestion of large amounts of vitamin D in association with a high intake of calcium. Postmortem examination could not be made. The clinical evidence, however, points most strongly to vitamin D intoxication as the cause of death.

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This report will be objected to. We may not be able to attribute the death to vit D intoxication

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# IDIOPATHIC HYPERCALCEMIA OF INFANCY, WITH FAILURE TO THRIVE*

## Report of Three Cases, with a Consideration of the Possible Etiology

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PHILADELPHIA

THE syndrome of "idiopathic hypercalcemia of infancy, with failure to thrive" has been reported with some frequency in the United Kingdom during the past few years. It appears to be relatively uncommon in North America, only 2 cases having been recorded in some detail[1,2] and 2 others briefly noted.[3] The reasons for this discrepancy in incidence among two populations, similar in many ways, are not understood.

Three infants with this condition, which was severe in 1 and mild in 2, have been observed at the Children's Hospital of Philadelphia within a period of two years. This communication is presented to focus attention on this disorder of infancy, lest it be more common, but unrecognized, in the United States, and to relate the observations concerning these 3 cases to the published reports from England, with particular consideration of the possible etiology.

## CASE REPORTS

CASE 1. K.S., an 11-month-old female infant, was first seen for the diagnosis and treatment of "dwarfism" and poor weight gain (Fig. 1). She had weighed 2.3 kg. (5 pounds, 1 ounce) at birth and had not been fed at the breast. The estimated daily intake of vitamin D before the initial examination was 1400 international units daily. She consistently refused solid foods and had a poor appetite. She gained weight and grew satisfactorily until 3 or 4 months of age, after which she failed to thrive (Fig. 2).

Physical examination revealed a malnourished infant who was irritable and possessed a peculiar elflike facies, with sparse hair on the head. There were prominent epicanthic folds, as well as an overhanging upper lip, and the bridge of the nose appeared to be underdeveloped for the age, as did the mandible. There were no teeth. There was a paradoxical combination of apparent disinterest in her environment with a rather alert countenance, as well as a degree of muscular activity that was greater than would be expected in the face of a generalized moderate hypotonia. She could support her head and was able, with some difficulty, to sit and to pull herself to a standing position. She had generalized pruritus and was covered with scratch marks. She weighed 5 kg. (11 pounds) and was 65 cm. tall; the upper-to-lower-body ratio was 1.55, and the circumference of the head was 41 cm., that of the chest 35 cm., and that of the abdomen 30 cm. A loud systolic murmur was audible over the entire precordium and was transmitted to the left posterior aspect of the thorax.

The blood pressure was 130/90.

Examination of the blood showed a red-cell count of 2,270,000, with a hemoglobin of 7.4 gm. per 100 ml., and a white-cell count of 9450, with 49 per cent neutrophils, 23 per cent lymphocytes, 6 per cent monocytes and 2 per cent eosinophils. Urinalysis revealed a specific gravity of 1.010, a pH of 7.0 and a trace of albumin and a ++ test for acetone; the sediment contained 4 or 5 white cells per high-power field. A culture of a specimen of urine obtained by catheterization indicated the presence of *Escherichia coli* and *Proteus vulgaris*. The chemical examinations of the serum are shown in Table 1.

Trypsin was present in the stool. Subdural taps were negative. Radiologic examination of the long bones revealed an abnormal density throughout, which was especially marked in the zones of provisional calcification, resembling osteopetrosis (Fig. 3), and increased density at the base of the skull (Fig. 4). An intravenous pyelogram showed poor dye concentration but the silhouette was adequate to rule out any abnormality; there was stippling in both renal shadows suggestive of renal calcinosis.

All supplemental vitamin D was discontinued, and feeding with unfortified whole cow's milk containing Karo syrup was instituted. The infant was then discharged on 500 mg. of chloramphenicol daily.

At 12 months of age the serum calcium rose to 15.0 mg., and the nonprotein nitrogen to 108 mg. per 100 ml. Treatment with 20 mg. of cortisone acetate daily, in divided doses by mouth, was instituted.

At 15 months of age, the weight had risen to 5.5 kg. (12 pounds, 3 ounces), and the patient was 66 cm. tall. The serum calcium was 14.0 mg., and the nonprotein nitrogen 85 mg. per 100 ml.

She weighed 5.8 kg. (12 pounds, 14 ounces) at 16 months of age and had progressed more in the previous 8 weeks than in any similar period since the onset. The cortisone treatment had been continued. She was less irritable, and the pruritus had diminished. The blood pressure was 130/90 to 160/120. The serum calcium was 9.6 mg. and 11.8 mg. on 2 successive days, and the nonprotein nitrogen 83 mg. per 100 ml. The serum phosphorus was 6.1 mg. per 100 ml. Owing to difficulties in obtaining unfortified cow's milk, the formula was changed to the following: strained beef, 312 gm.; Dextri-Maltose, 71 gm.; olive oil, 100 ml.; and water, 1080 ml. The dose of cortisone was diminished to 10 mg. daily.

At 22 months of age, the patient weighed 6.6 kg. (14 pounds, 8 ounces). The serum calcium was 10.5 mg., and the nonprotein nitrogen 54 mg. per 100 ml.

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Two months later she weighed 7 kg. (15 pounds, 8 ounces) and was 61 cm. tall. The cardiac murmur persisted. X-ray study of the chest revealed a normal cardiac silhouette, and there had been no other clinical evidence of organic heart disease. She had become playful and happier (Fig. 5) and spoke three or four words. The serum calcium was 10.8 mg., and the phosphorus 4.1 mg. per 100 ml.

FIGURE 1. *Appearance of Case 1 at Eleven Months of Age.*

At 27 months of age she was readmitted to the hospital for detailed examination. The blood pressure had fallen to 128/60. The murmur persisted. The serum bicarbonate was 20 milliequiv. per liter, and the calcium was 11.6 mg., the phosphorus 5.5 mg., and the cholesterol 256 mg. per 100 ml. There was a total of 20.7 mg. of calcium in a 24-hour specimen of urine — this was determined after 11 months on a low-calcium diet. Radiologic examination indicated a diminution of the osteosclerosis, with no evidence of rickets; the calcification of the falx cerebri was again noted, and the sagittal suture of the skull was completely united. The bone age determined at multiple centers was 2 to 2½ years. The patient was discharged on a smaller dose of cortisone (5 mg. daily), with continuation of the antibiotics.

At 29 months of age she weighed 7.7 kg. (17 pounds) and was 75 cm. tall. The blood pressure was 120/70. There was a great change in her general appearance, with a subsidence of the facial features noted earlier and an increase in subcutaneous fat. She was walking fairly well, but with support. At 33 months of age there was continued improvement in her general appearance, but there appeared to be moderate retardation of intellectual development. The serum calcium was 11.3 mg., and the phosphorus 5.6 mg. per 100 ml.

CASE 2. L.L., an 18-month-old male infant, was first seen for consideration of "growth failure." An older female sibling had always been healthy. The patient had been born 1 month prematurely and weighed 2.2 kg. (4 pounds, 14 ounces) but appeared healthy. He was not fed at the breast. The total daily intake of vitamin D was calculated to approximate 2500 international units. Between the ages of 4 and 8 weeks projectile emesis occurred once a day, ceasing after a time, but since then he had gained weight and height poorly. The parents described marked polyuria and polydipsia. He had received an unknown dose of desiccated thyroid between the ages of 12 to 14 months, with no improvement. He had always shown a disinclination toward solid foods.

Physical examination demonstrated the peculiar elflike facies noted in Case 1; the similarity was at once striking (Fig. 6). A soft systolic murmur was distinctly audible at the apex but was not transmitted.

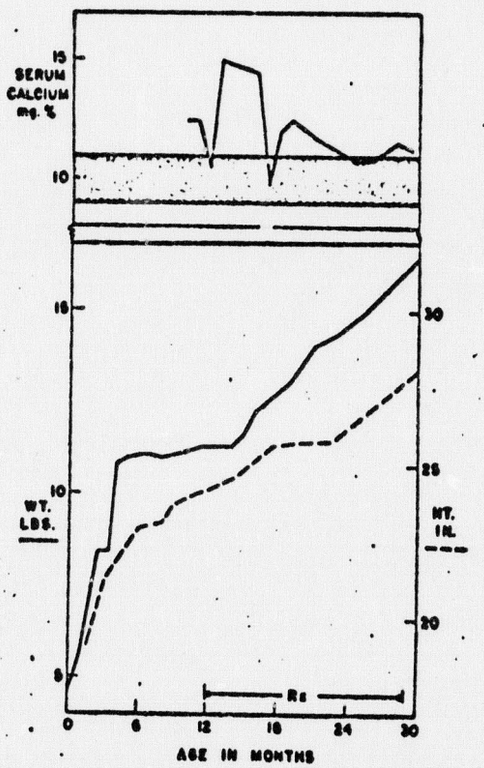


FIGURE 2. *Progress of Case 1 since Birth, Showing Growth Failure at the Time of Onset and Serum Calcium Levels. Treatment consisted of a diet low in calcium and vitamin D, with cortisone.*

The patient was admitted to the hospital at 20 months of age, when he weighed 7.5 kg. (16 pounds, 9 ounces) and was 74 cm. tall. The blood pressure was 120/70. Generalized hypotonia was present. The laboratory data are summarized in Table 1. The protein-bound iodine was 8.6 microgm. per 100 ml. The bone age was 13 months; there were no abnormalities of the long bones or skull, and calcification in the renal area was not noted.

The patient was discharged on a low-calcium diet utilizing a beef-base formula as in Case 1. All vitamin D supplements were discontinued.

Ten weeks later he was walking alone, and his appetite had improved. The serum calcium was 12.3 mg. per 100 ml.

At 2 years of age, the serum calcium was 11.9 mg. per 100 ml. There was marked improvement in muscular strength and appetite. He weighed 7.8 kg. (17 pounds, 4 ounces) and was 75 cm. tall.

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CASE 3. M.S., a 13½-month-old male infant, was first seen because of poor growth. A male sibling, 4 years of age, had always been well. The patient weighed 3.7 kg. (8 pounds, 3 ounces) at delivery. He was not breast fed. At 9 months of age he weighed 8.2 kg. (18 pounds). He then became listless, mild anorexia developed, and he gained very little weight during the subsequent 4½ months. There was no history of excessive intake of vitamin D, and it was estimated that he received about 1200 international units daily. He sat alone at 6 months, crawled at 10 months and was able to stand without support at the time of the 1st examination.

On physical examination at 13½ months he weighed 8.6 kg. (19 pounds) and was 75 cm. tall; the circumference of the head was 48 cm., that of the chest 46 cm., and that of the abdomen 42 cm. The facies was vaguely suggestive of that described in Cases 1 and 2. He was active in his crib but unable to move around to any extent because of a distinct generalized hypotonia. The heart, lungs and abdomen were normal.

Examination of the blood showed a red-cell count of 3,550,000, with a hemoglobin of 13.1 gm. per 100 ml., and a white-cell count of 8500, with 38 per cent neutrophils, 56 per cent lymphocytes and 6 per cent monocytes. Urinalysis indicated a specific gravity of 1.027 to 1.030, a pH of 4.5 to 7.0, a + + to + + + + test for acetone, a + + Sulkowitch test and no phenylpyruvic acid; there were no white cells in the sediment. Radiologic study revealed bones of normal density and a normal bone age. The protein-bound iodine was 5.8 microgm. per 100 ml. Certain laboratory data are shown in Table 1. The urinary calcium was 30.2 mg. per day, and the phosphorus 273 mg. per day. The spinal fluid was normal. The Kolmer test was negative. The patient was discharged on a diet without additional vitamin D and with no attempt to restrict calcium intake. Two months later the serum calcium was again 12.0 mg., and the phosphorus 3.1 mg. per 100 ml.

## Discussion

In 1932 Lightwood[4] probably first described what has since been termed "idiopathic hypercalcemia of infants, with failure to thrive."[5] The child discussed at this relatively early date presented most of the clinical features associated with the severe form of the syndrome. The findings were not associated with a high intake of vitamin D. The patient died, and postmortem study showed renal calcinosis and osteopetrosis.

The problem was recalled in 1951, when Fanconi[6] and Butler[7] simultaneously presented their observations on 1 infant each, remarking on the coincidence of growth failure, hypercalcemia and certain other clinical features detailed below. Subsequently, these authors and their co-workers presented a detailed joint report.[8] In 1952 Lightwood and Payne[9] described 10 infants with hypercalcemia and failure to thrive, whom they delineated from the syndrome of "renal acidosis." Since then, numerous cases have been reported in the British literature but only 4 in the American.[1-3]

The symptoms and clinical features of idiopathic hypercalcemia of infancy with failure to thrive present a constant pattern in the various reports cited. There is no sex difference. The onset of the clinical manifestations, particularly the cessation of growth, is between six weeks and nine months of age. Case 2 is said to have been thriving poorly since birth. There may be marasmus in the severe form of the disorder. Gastrointestinal complaints are common and include emesis (often projectile), anorexia and constipation. Polyuria and polydipsia (reported only in Case 2) occur in about 50 per cent. There is generalized muscular hypotonia in almost all patients, and this frequently misleads the examiner into believing that the child is mentally retarded. Paradoxically, most children are alert and not sluggish in spite of the hypotonia. The facies has been described as "elflike," with prominent epicanthic folds, overhanging upper lip and underdeveloped bridge of the nose and mandible; these features were distinctive in Cases 1 and 2. However, the characteristic facies may be absent.[8] In about 40 per cent there is hypertension. A harsh systolic cardiac murmur is audible in many and has not been attributable to cardiac disease — Lowe et al.[10] found extensive metastatic calcification, including the heart and lungs, in 1 case. Transient facial palsies may occur, and nonparalytic squint is sometimes present. The head may fail to grow during the active stage of the disease.

The chemical findings described in 10 infants by Lightwood and Payne[8] have been noted regularly. The serum calcium is elevated, and the levels above 11.5 mg. per 100 ml. are significant[11] when persistent and accompanied by the other features. The blood urea nitrogen is sometimes elevated, but the serum phosphorus, phosphatase, bicarbonate and chloride are usually normal. The serum alpha$_2$ globulins and gamma globulins are often elevated. Other biochemical findings[11] include an elevated serum cholesterol in 60 per cent at some time during the stage of the disease; this was true in Case 1 only. The serum phosphorus may rise with continued progress of the disease in the severe form. The serum alkaline phosphatase is almost never elevated and may be low in 40 per cent.

Nephrocalcinosis was detected in approximately 20 per cent of the reported cases. Intravenous pyelograms reveal no abnormality, other than poor concentration of the dye.[2] There is increased density of the long bones and the base of the skull, resembling true osteosclerosis (Albers–Schönberg disease), in 20 per cent, and in a larger number there are only transverse lines of increased density in the long bones. Craniostenosis may occur in 10 to 20 per cent of cases with the severe form of the disorder. Evidence of renal infection is present in about 50 per cent of cases.

A distinction has been drawn between a benign and a severe form of idiopathic hypercalcemia of infants, and this has been sharply defined by Lowe et al.[10] The benign form is said to be transient, self-limited and subject to relatively early remission with no permanent consequences; the severe form is more protracted and may be fatal, or with remission there is mental and physical retardation. The characteristic facies is absent in the benign form. Hypertension, heart mur-

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mur and osteosclerosis are supposedly confined to the severe type. There may be a more marked elevation of the serum calcium, blood urea nitrogen and cholesterol in the severe type. In the 3 cases described above, it was not possible to classify sharply each child on the basis of this group of findings. On the basis of the biochemical findings, Rhaney and Mitchell[9] take exception to the formulation of definite criteria for such a distinction; 4 of their patients with the "benign" form died. A loud heart murmur may occur in the "benign" form, and osteosclerosis may be absent in the "severe" form. There appear to be all gradations of severity, and it is difficult to assign patients to one group or another. On a clinical basis, only Case 1 may be termed "severe."

Each of the patients described above was referred to the Children's Hospital of Philadelphia because of growth failure. The differential diagnosis merits some discussion. Although the presence of an elevated serum calcium will focus attention on the diagnosis of idiopathic hypercalcemia, other causes of growth failure should be sought.

Certain other conditions more closely related to the syndrome of idiopathic hypercalcemia require special attention.[10-16] Hyperparathyroidism may be considered, but in this condition there is a diminution in serum phosphorus (at least in the early stages), a marked rise in urinary calcium above the levels reported in the syndrome under discussion and an increase of serum alkaline phosphatase; furthermore, the bone lesions of hyperparathyroidism generally differ from those described in idiopathic hypercalcemia. In idiopathic hypercalcemia the bone lesions may suggest Albers-Schönberg disease, but in that condition the serum reveals no biochemical changes and there is often a myelophthisic anemia and a family history of the disorder. True vitamin D intoxication may be recognized by the history of the ingestion of large amounts of this vitamin and by the decalcification of bone, as a rule, rather than osteosclerosis. Renal acidosis may closely resemble idiopathic hypercalcemia but can be readily differentiated: hypotonia does not occur in renal acidosis; acidosis is absent in idiopathic hypercalcemia but present in renal acidosis — the urine is always alkaline in the former, and usually acid or neutral in the latter; and the serum calcium may rarely be high in renal acidosis, but falls with alkaline therapy — it does not fall with such therapy in idiopathic hypercalcemia. Osteosclerosis may occur in both syndromes.

Idiopathic hypercalcemia of infancy is a self-limited disease, and spontaneous recovery is the rule. In the more severe forms death from renal insufficiency may occur, or if the patient survives, physical retardation may persist for some years and mental retardation, possibly owing to premature cranial synosteosis, may become apparent.

TABLE 1. *Data in 3 Cases of Idiopathic Hypercalcemia of Infancy.**

| Age at Onset | Elfinlike Facies | Vitamin D Dosage | Cardiac Murmur | Blood Pressure | Serum Calcium | Serum Phosphorus | Serum Cholesterol | Serum Nonprotein Nitrogen | Serum Sodium |
|---|---|---|---|---|---|---|---|---|---|
| mo. | | *international units* | | | *mg./100 ml.* | *mg./100 ml.* | *mg./100 ml.* | *mg./100 ml.* | *milliequiv./liter* |
| 4 | +++ | 1400 | +++ | 130/90-160/120 | 12.5-15.0 | 7.0-7.9 | 230 | 102-118 | — |
| 1 | ++ | 2500 | + | 120/70 | 11.7-12.5 | 5.5 | 198 | 30 | 142 |
| 8-9 | ± | 1700 | 0 | 108/70 | 12.0-13.0 | 3.5-4.9 | 138 | 33 | — |

*No infants breast fed.

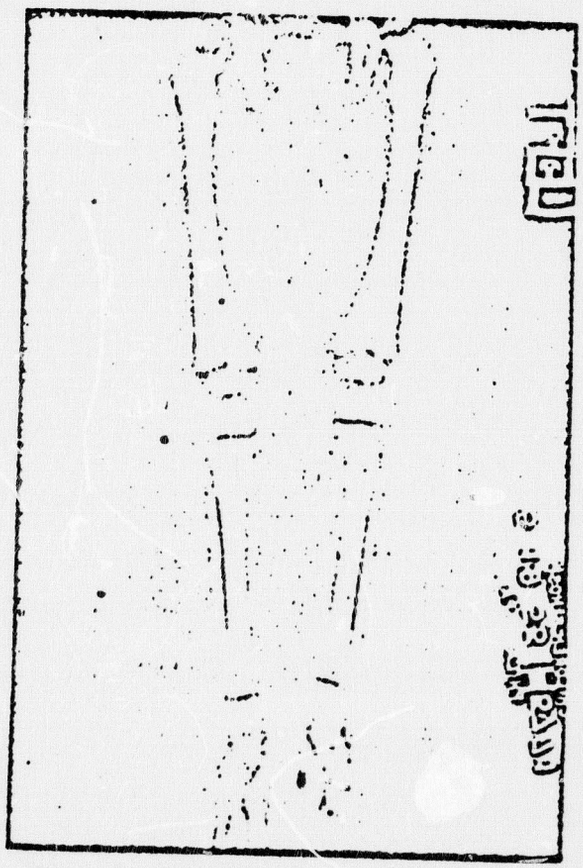

FIGURE 3. *X-Ray Film of the Long Bones in Case 1.*

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## Etiology

The cause of idiopathic hypercalcemia of infancy, with failure to thrive, is not established. Several factors have been incriminated, and, at present, sensitivity to vitamin D has been assigned a prominent role by many authors.

Fanconi[6] attributed the disease to a collection of separate congenital defects. Butler[8] believed the condition to result from an abnormal sensitivity to ingested calcium in the face of primary renal damage.

TABLE 1 *(Concluded).*

| Age at Onset | Serum Chloride | Serum Bicarbonate | Alkaline Phosphatase | Total Protein | Albumin | Alpha1 Globulin | Gamma Globulin | pH of Urine | Specific Gravity of Urine |
|---|---|---|---|---|---|---|---|---|---|
| mo. | * milliequiv./liter | milliequiv./liter | units | gm./100 ml. | gm./100 ml. | gm./100 ml. | gm./100 ml. | | |
| 4 | — | 20 | 6.9 | 8.1 | 3.3 | — | — | 5.0-7.0 | 1.010-1.020 |
| 1 | 103 | 21 | 3.5 | 7.2 | 5.0 | 0.9 | 0.7 | 6.0 | 1.014 |
| 8-9 | 103 | 23 | 3.5 | 6.9 | 3.5 | 1.1 | 0.7 | 7.0 | 1.027 |

*No infants breast fed.

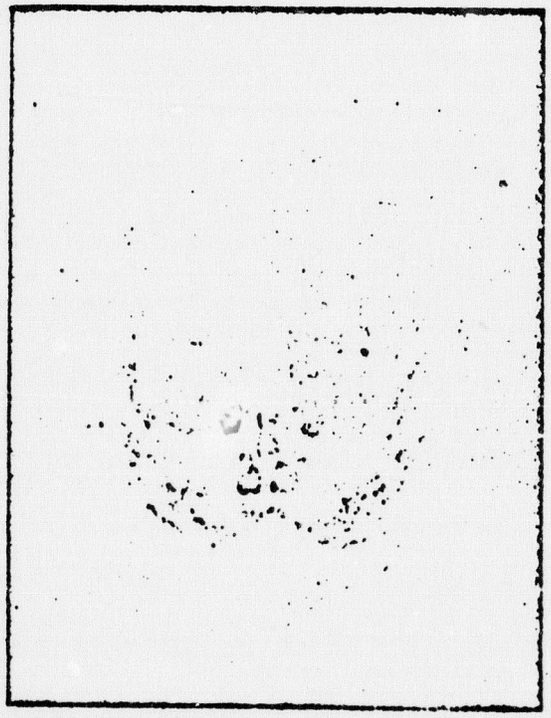

FIGURE 4. *X-Ray Film of the Skull in Case 1.*

It is improbable that parathyroid dysfunction is primarily responsible for this syndrome. As discussed above, the biochemical findings are not consistent with disease of the parathyroid glands; furthermore, examination of the glands[16,17] has shown them to be normal. It is possible that renal tubular immaturity, with unresponsiveness to parathormone, could produce hypercalcemia; however, it is possible to increase the urinary phosphate excretion in an infant with the syndrome by the administration of parathormone.[4,18]

The similarity of this disease to the "milk-alkali" syndrome in adults has led to consideration of the role of alkaline medications in infancy. Creery[18] pointed out that a high percentage of infants in his series had received alkaline laxatives or other remedies. In 1 American case[1] the frequent use of alkali was also reported. However, many patients received no such treatment. It is improbable that the ingestion of alkali is the sole cause of the disorder, although it cannot be denied that in occasional infants such therapy may aggravate an otherwise subclinical form. Creery and Neill[19] have suggested that renal infection per se may lead to hypercalcemia in certain children. There are many cases, generally milder, in which there has been no evidence of urinary infection, but it is possible that an earlier infection has subsided before the infant is brought under close scrutiny.

Forfar et al.[12] have described an increased calcium retention in 3 cases — 31, 48 and 69 per cent (normal, 32 per cent); others[3,10,14] have reported similar findings. Phosphorus retention is also increased.[12] Mild hypercalciuria is present in some cases.[13] The urinary amino acids are normal.[20]

Impaired renal function is evident from the frequent elevation of serum urea nitrogen or nonprotein nitrogen. This tends to subside with improvement in all but the severe cases. Fanconi[6] observed diminished renal clearance in a severe case. Sissman and Klein[3] conclude that dehydration may be the cause of the elevation of the nonprotein nitrogen; they also reported a low-normal tubular reabsorption of phosphate. In fatal cases renal calcinosis has been observed.[4,6,11,17]

Although definitive proof that vitamin D is the major cause of idiopathic hypercalcemia in infancy is lacking, there is much evidence to warrant serious attention to such a possibility. In most cases reported, the intake of vitamin D is not generally considered to be excessive; indeed, 3 of the 5 patients described by Forfar et al.[12] had received 400 to 550 international units daily, which is less than the recommended amount in the United Kingdom. Aside from the dis-

similarities between idiopathic hypercalcemia and classic vitamin D intoxication discussed above, the serum citrate levels have been shown to be depressed,[12] a finding inconsistent with true vitamin D intoxication.

Is there a hypersensitivity to ordinary quantities of vitamin D in these infants? What constitutes an excessive intake? The former question has been raised

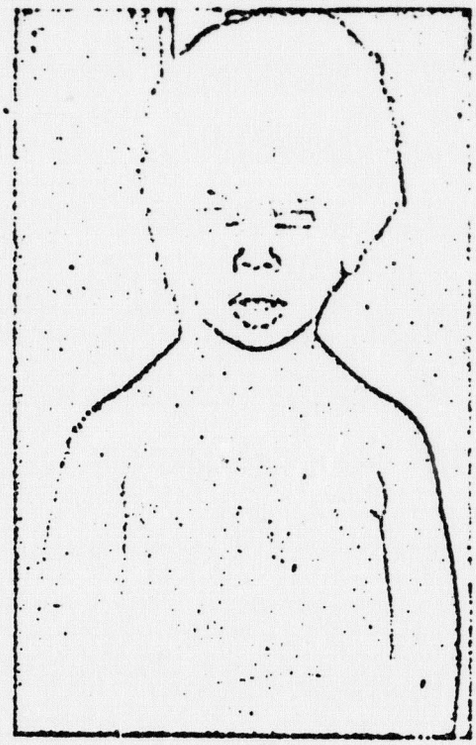

FIGURE 5. *Case 1 at Two Years of Age.*

in view of the failure to elicit by history an ingestion of what may be considered a large amount of the vitamin. Fyfe[21] has shown that the blood levels after oral administration are much higher in infants with idiopathic hypercalcemia than in normal infants. Might the same phenomenon occur in certain infants after "ordinary" doses of vitamin D? Perhaps the concepts of ordinary or extraordinary amounts of vitamin D require better definition. In a review, Jeans[22] pointed out that 200 international units of vitamin D daily produced a degree of calcium retention in infants no greater than that obtained when 800 units or more was used — at the higher level anorexia, diminished intake of food and failure to thrive developed.

Before 1943 the conventional dosage of vitamin D in England was 400 international units daily; more recently, coincident with the rise in frequency of idiopathic hypercalcemia in England, the official recommendation has been 700 units per day[12]; in addition, during this period, milk in the United Kingdom has been fortified with 1400 international units of vitamin D per quart whereas in the United States the amount is 400 units per quart. Might this seemingly inconsequential change account for the apparent difference in incidence between the two countries? Creery and Neill[20] state that no case of idiopathic hypercalcemia has occurred in "completely" breast-fed infants. None of our 3 patients were breast fed. However, some infants have been breast fed for variable, but perhaps inadequate, periods.[17] If vitamin D bears some responsibility for the condition, the fortification of artificial formulas and cow's milk requires careful scrutiny. It has been suggested[23] that the total vitamin D intake in infancy be limited to 400 to 800 international units per day — certainly, this is adequate.[22] The fortification of milk, bread, virtually all infant cereals and artificially prepared

FIGURE 6. *Appearance of Case 2 at Eighteen Months of Age.*

commercial formulas in the United States is enthusiastically practiced. The practice seems to have got out of hand, and the quantities of added vitamins are frequently the focus of competitive advertisement. This fact was forcibly impressed upon us when we searched for foodstuffs containing little or no vitamin D for the treatment of the cases reported above. In the Philadelphia area it was almost impossible to obtain milk free of vitamin D.

Forfar et al.[12] have proposed an abnormality in the metabolism of cholesterol, the production of abnormal toxic sterols with vitamin D activity, as the basic cause of the disorder. Certain observations suggest that vitamin D may not be the major etiologic agent in

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pathic hypercalcemia. Hubble[18] administered large doses (550,000 and 1,000,000 international units) to 2 infants in remission, without producing a relapse; perhaps a temporary period of vitamin D hypersensitivity had already elapsed. The same authors[17] gave calciferol to infants during the active phase of the disease, without exaggerating the clinical features or the calcium retention. One infant in remission[20] received 2000 international units of vitamin D daily; within two weeks the serum calcium and blood urea nitrogen rose slightly but fell thereafter. In a similar experiment during remission,[24] an exacerbation was produced.

## Treatment

Creery and Neill[20] obtained good results by employing the usual diet containing unfortified milk and without added vitamin D. The more thorough removal of vitamin D from the diet has been recommended by others.[10] In addition, the employment of a calcium-free diet has produced a depression of the serum calcium level.[24] Stapleton, Macdonald and Lightwood[14] believe that the use of a calcium-free diet and removal of all sources of vitamin D accelerate the rate of recovery.

It has been stated that cortisone ordinarily causes an increased excretion of calcium and phosphorus.[25] Striking improvement has been described in 1 infant with severe idiopathic hypercalcemia after the administration of 12.5 mg. of cortisone daily.[20] An increase in the excretion of calcium and phosphorus has been reported to follow the use of cortisone for idiopathic hypercalcemia.[13]

As would be expected, various agents that "bind" calcium, and thus increase renal excretion or interfere with intestinal absorption, have been tried. Lowe et al.[10] observed no beneficial effect on the serum calcium level after the oral administration of sodium ethylenediaminetetracetate; another patient died after the intramuscular administration of this compound. It is not recommended for the treatment of idiopathic hypercalcemia.

Sodium phytate (a salt of inositol hexaphosphoric acid) forms insoluble salts with calcium and has been employed to block the intestinal absorption of calcium in vitamin D poisoning and sarcoidosis by Henneman and Carroll.[26] Carter et al.[24] have attempted to employ "all-bran" as a source of phytic acid in infants with idiopathic hypercalcemia. This agent appears to be relatively free of undesirable effects. We are currently administering it to one baby (Case 2) in an attempt to hasten recovery.

The employment of sulfonamides for the concomitant urinary infection is probably contraindicated. Harris[27] has shown that they may aggravate renal damage and osteosclerosis. Although it is advisable to employ other suitable treatment for the urinary infection, Lightwood and Payne[5] do not believe that such therapy hastens the remission of the hypercalcemia.

## Summary and Conclusions

Three cases of "idiopathic hypercalcemia of infancy, with failure to thrive," occurring within a two-year period in a single children's hospital in the United States, are described. The condition has been seen much more commonly in the United Kingdom, although it is possible that it is not always recognized in North America. The role of vitamin D is discussed. The more moderate use of vitamin D in infant nutrition is advisable. When the condition occurs, it is best treated with a diet low in calcium and vitamin D. If the condition is severe, small doses of cortisone may be employed.

Idiopathic hypercalcemia of infancy, with failure to thrive, is a distinct clinical entity of unknown cause, although it appears highly probable that vitamin D has an important role in the etiology. This syndrome is not synonymous with true vitamin D intoxication, but it may represent an expression of hypersensitivity to vitamin D in certain infants.

Whether or not idiopathic hypercalcemia of infancy with failure to thrive is truly uncommon in the United States, it behooves the American physician to take warning and to avoid the excessive use of vitamin D. Moderation should be practiced in the commercial houses entrusted with the preparation of infant foods. It is likely that 400 or 500 international units of vitamin D per day is adequate for almost all infants. It would be desirable to obtain better control over the intake of infants exposed to so many sources in a "vitamin-hysterical" environment. The physician and parent, unfortunately, are not always aware of an infant's total vitamin D intake. It is virtually impossible under present conditions to determine the contribution from various "hidden" sources.

We are indebted to Drs. Anthony J. Repici, Paul Morris and Henry S. Cecil for the opportunity of studying these cases.

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# PRESENCE OF CHILDREN IN THE HOUSEHOLD AS A FACTOR IN THE INCIDENCE OF PARALYTIC POLIOMYELITIS IN ADULTS*

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IN a recent study on poliomyelitis and pregnancy, a relation was observed between the occurrence of poliomyelitis during gestation and parity.[1] Regardless of maternal age, clinical infection was more frequent in multiparous than in primiparous women. The association between parity and poliomyelitis appeared to be dependent, in part, on the number of children in the household. However, the relation could not be explored further because no data on the distribution of the general population by family size were available. They have become available since then.

TABLE 1. *Annual Incidence of Poliomyelitis, New York City, 1949-1953.*

| YEAR | ALL AGES | | AGE GROUP 15-44 YR. | |
|---|---|---|---|---|
| | NO. OF CASES | RATE PER 100,000 | NO. OF CASES | RATE PER 100,000 |
| 1949 | 2446 | 31.0 | 524 | 14.6 |
| 1950 | 1064 | 13.5 | 277 | 7.5 |
| 1951 | 555 | 6.8 | 119 | 3.3 |
| 1952 | 821 | 10.2 | 218 | 5.9 |
| 1953 | 677 | 8.5 | 161 | 4.4 |
| Totals | 5563 | 14.0 | 1299 | 7.1 |
| Percentage | 100.0 | | 23.4 | |

Studies of poliomyelitis in households have been conducted by a number of investigators. Some of the earliest works were on the frequency of multiple cases in households. These indicated that most of the patients with so-called "secondary" cases were infected at the same time as the patient with a "primary" case, presumably from a common carrier source.[2-9] Laboratory studies by other investigators confirmed these clinical impressions. They revealed the rapidity with which the virus was spread among the members of a household, and the importance of the affected household as a source for the dissemination of virus in the community.[10-18] The intestinal tracts of persons infected for the first time were found to be heavily seeded with virus, even among those who had been actively immunized with Salk's formalin-treated virus vaccine.[19-25]

The present study was undertaken to investigate the influence of children in the household on the incidence of paralytic poliomyelitis in adults, taking into consideration the factors of age, sex, marital status and pregnancy. Since 99 per cent of patients in all reported cases of poliomyelitis in the adult group were fifteen to forty-four years of age, the study was limited to this age group.

TABLE 2. *Distribution of Cases According to Clinical Type.*

| CLINICAL TYPE | NO. OF CASES | PERCENTAGES |
|---|---|---|
| Nonparalytic | 366 | 28.2 |
| Spinal paralytic | 644 | 49.6 |
| Bulbar paralytic | 289 | 22.2 |
| Totals | 1299 | 100.0 |

The data on the occurrence of poliomyelitis in the population under consideration were obtained from the clinical and epidemiologic investigation of cases reported to the City of New York Health Department from 1949 to 1953, inclusive. The information was obtained by epidemiologists, who visited all patients

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# AN EXPERIMENTAL HISTOLOGIC STUDY OF HYPERVITAMINOSIS D.*

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Soon after the discovery of the similarity of Vitamin D to irradiated ergosterol, several investigators became concerned with the action of excessive doses of irradiated ergosterol.[1-5] It was generally agreed that the compound exerted its effects by its influence upon calcium and phosphorus metabolism, presumably through some intermediary hormonal mechanism.[6,7] It was proved that the compound had no serious toxic action except when given in doses far in excess of those required for prevention or cure of rickets due to a deficiency of Vitamin D.[8] Finally, it was established that the principal pathologic changes attributable to excessive doses in man or animal were in the form of abnormal deposits of calcium in many organs and tissues.[9-11] Having settled practical matters concerning the clinical use of the compound, interest in hypervitaminosis D subsided, and except for the studies of Follis, little attention has been given to the subject since 1935.[12,13]

Our interest in hypervitaminosis D arose as a result of the emphasis of Wolbach, Bessey and Fell upon the use of avitaminoses and hypervitaminoses as tools for study of pathologic sequences and their relations to the locus or nature of action of vitamins.[14-18] Sequences in human disease with which we have been concerned relate to so-called degenerative changes which are especially conspicuous in connective tissues and more common in arteriosclerosis than in any other human disorder.[11,19] The lesions described in hypervitaminosis D seemed to offer a promising source of information in further study of these non-inflammatory degenerative sequences.[2-5,8] Hence, histologic studies of

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the distribution and evolution of lesions in rabbits given excessive doses of irradiated ergosterol were undertaken with special attention to changes in the vascular system.

## Methods

The viosterol used in the experiments was a solution of irradiated ergosterol (15 mg. per ml.) in peanut oil. (Abbott Laboratories, Chicago, Ill.) The potency was assayed as about $10^6$ U.S.P. units per ml. This was given intramuscularly in doses of 0.1 ml. ($10^5$ U.S.P. units) at daily, biweekly or triweekly intervals for periods as long as 6 to 8 weeks. The regime was varied at lower dosages so that minimal and maximal pathologic effects could be defined and their evolution recognized over a period of several months.

Male albino rabbits from a single stock, about 5 pounds in weight and 3 months old, were used. Records of weight and analyses for serum calcium, phosphorus and cholesterol were made at intervals of about 2 weeks. The animals were fed a Purina Rabbit Pellet diet with fresh vegetables. For control purposes, complete microscopic studies were made of 75 normal rabbits from the same stock, of the same age and maintained on the same diet.

Since the initial plan was to produce maximal pathologic effects, the dose was regulated at levels just below the quick lethal range. Hence, most animals lost weight and died within 6 weeks. Later, the plan was to analyze minimal, sublethal and early pathologic effects, and animals were either sacrificed at any early stage or given viosterol at longer intervals and sacrificed at a later stage. Complete necropsies were done and a record of the gross findings made. All tissues and organs were fixed in formaldehyde (4 per cent U.S.P.) and studied microscopically. A series of 54 animals were suitable for the purposes of this report, with 49 additional animals on other dietary and viosterol regimes available for supplementary and confirmatory observations.

## Results

### Gross Pathologic Changes

The pathologic processes attributable to hypervitaminosis D varied with the dosage of viosterol, the length of the period between doses, duration of the regime, and the occurrence of intercurrent infections.

Minimal conditions for production of significant generalized calcinosis were a duration of 8 days and a total of 300,000 units given in 3 equal doses at intervals of 2 days. These conditions were usually complicated by intercurrent chronic purulent pyelonephritis of a type occasionally encountered in control animals. Among animals free

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from extraneous disease, except hepatic coccidiosis, the total minimal effective dose was 500,000 to 600,000 units. This dose produced generalized calcinosis of increasing severity as the time of administration in periodic equal doses was extended to at least 3 weeks. The severity of the disease was further increased as the biweekly administration of doses of 100,000 units was continued beyond 3 weeks. This regime generally led to anorexia, loss of weight and death within about 6 weeks. Accurate control of the rate of development of pathologic processes was also obtained, so that prolonged participation of tissue elements in mechanisms of resorption, repair and regeneration might be studied, but this required careful regulation of dosage over a period of about 6 months.

Significant gross anatomic changes were encountered only in animals with considerable disease, manifest by changes in bones or deposition of calcium in numerous extra-osseous tissues. These could not be correlated with any consistent changes in values for cholesterol, calcium, or phosphorus in the serum.

The changes in bones varied with the severity and duration of disease. In general, the bones were more brittle than normal (Fig. 9). The increased fragility was due largely to resorption of cortical bone, often sufficient to allow mechanical deformity of bodies of vertebrae so that partial collapse and abnormal cortical contours were occasionally conspicuous. In these cases, the trabecular structure was compact and the marrow spaces reduced so that the internal structure of the vertebral bodies resembled that found in human osteosclerosis and Paget's disease (Fig. 10).

The amount and distribution of abnormal deposits of calcium in extra-osseous tissues also varied with the duration and severity of the disease. In mildly affected animals there were no gross changes. With increasing severity of the disorder, calcium salts began to appear as white streaks which acquired an opaque brittle or granular character. The deposits conformed to anatomic planes and structural outlines of affected tissues. They were most conspicuous in the aorta and its major branches, being maximal proximally and diminishing distally in a consistent pattern.[2,20] The deposits were in the media, usually in the form of continuous sheets or as a series of discontinuous rings with aneurysmal deformities of the wall. Calcium deposits were less conspicuous in the kidney, where bandlike granular deposits, were noted, first in the inner cortex and later, as the calcified zone of the innermost cortex spread toward the capsule, as one or more convex parallel bands in the periphery of the medulla (Fig. 7).[4]

The next most common location of calcium deposits was in muscle (Fig. 2). The deposits coincided with white streaks which followed the pattern of orientation of muscle cells or distribution of arteries. They were less common in skeletal than cardiac muscle, but frequently were clearly distinguished in the diaphragm and smooth muscle of special parts of the alimentary tract. The esophagus was never affected. The walls of the ileum and colon were occasionally altered, but this never occurred unless there were extensive deposits in the muscular wall of the stomach subjacent to the acid-secreting mucosa (Fig. 5). The acid-secreting gastric mucosa also commonly contained deposits of calcium but less frequently than the subjacent musculature. Calcium deposits were not found in the mucosa or muscle of those parts of the stomach which have no acid-secreting function.

Another common location of calcium deposits was in the respiratory tract. The tracheal and bronchial cartilages were often rigid and calcified, and thin plaques of calcium were at times recognized in the mucosa of the larger respiratory passages. Calcium deposits were rarely found in the media of large pulmonary arteries but were fairly common in the walls of pulmonary veins. In connection with these changes, pulmonary emphysema and decreased elasticity of the alveolar structure were usually demonstrable.

Other tissues and organs occasionally contained gross traces of calcium salts, but in many locations the presence of the mineral deposits was established only by microscopic studies.

## Microscopic Pathologic Changes

### *Heart*

Deposition of calcium in the heart was usually associated with a peculiar inflammatory reaction similar to that described in rats (Fig. 1).[1,8] In general, the calcification potential of various cardiac structures in order of decreasing intensity and frequency was as follows: internal elastic membrane of coronary arteries, smooth muscle of coronary arteries, fibroelastic tissue of the endocardium, and cardiac muscle. Calcium deposition in cardiac muscle cells was confined initially to the "A" disks of the myofibrils. As the amount of calcium increased, the "I" disks were involved, and later the interfibrillar compartment was affected so that the muscle cell appeared to be impregnated uniformly with calcium. At times, as much as one third of the myocardium was involved, but as a rule the calcified muscle cells were distributed irregularly around the coronary arteries or in the subendocardial region (Fig. 2). This localization seemed to be determined partly by the

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common occurrence of a low-grade inflammatory reaction (Fig. 1). At times, the reaction was principally in the form of arteritis and periarteritis, characterized by swelling of collagen, perivascular proliferation of histiocytes, and formation of focal nodular lesions which resembled Aschoff bodies. Usually these lesions lay either adjacent to or around cardiac muscle cells in various stages of degeneration, calcification, and resorption. Their incidence increased with the level of dosage of viosterol and perhaps with the intrusion of intercurrent infections, though data concerning the role of infections were too meager to justify final conclusions. Suffice it to say that control animals dying of the same infections had no lesions of the type described.

The presence of an active periarteritis and myocarditis may have had something to do with the distribution of calcified cardiac muscle cells, but there seemed to be little relation between the inflammatory reactions and calcification of the media of coronary arteries. The main coronary arteries were free from inflammation, and calcium deposits in the internal elastic membrane or smooth muscle of the media were more conspicuous in these vessels than in the smaller intramyocardial branches which exhibited inflammatory reactions. In some instances, the deposition of calcium was so great that it was detectable in coronary arterial branches of all dimensions. This process was never uniform in arteries of equal dimensions but involved certain arterial branches more severely than others.

Calcification of the fibrous or fibroelastic stroma of the heart was never impressive in valves or in the myocardium. The endocardium, especially of the left atrium, was occasionally severely calcified, the process being more pronounced in elastic networks than collagenous fibrils.

### *Respiratory Tract*

The sequences and pattern of calcification in the respiratory tract were of great interest. The earliest deposition, other than that occurring in the tracheobronchial cartilages and goblet cells, was in the fibroelastic stroma of the tracheal mucosa. The calcium deposits were distributed at regular intervals just below the basal layer of epithelial cells. As a rule, the basement membrane and underlying fibroelastic tissues were affected. In more advanced cases, the deposits involved the entire basement membrane and variable amounts of subjacent fibroelastic tissue, as deep as the plane of the mucosal vascular plexus (Fig. 3). Only rarely did the calcium deposits extend in continuity from basement membrane to the perichondrium of cartilaginous rings. Invariably, however, in these severe lesions there was excessive calci-

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fication of the cartilaginous matrix. When this occurred, the calcified zones of cartilage lay adjacent to those of the mucosa, and at times there was erosion and stromal penetration of the margins of calcified cartilage. This was not followed by osteogenesis. On the contrary, the stromal invasion stimulated resorption of mineralized matrix and regional proliferation of young cartilage cells.

Calcification of the subepithelial tracheobronchial stroma was often preceded or accompanied by swelling and distortion of collagenous fibrils, but customary signs of inflammation were usually absent. However, once calcification had occurred, reparative sequences were at times recognized. These seemed to be initiated by two factors. One was the fragmentation of calcified fibroelastic tissue and basement membranes, leading to local proliferation of histiocytes and encapsulation of displaced degenerated calcified tissue by histiocytes and multinucleated giant cells. As this occurred, the subepithelial basement membranes and adjacent mucosal stroma were usually slowly regenerated. When the reparative process was unduly active, the epithelium regressed to an undifferentiated type of columnar cells which regenerated as either a characteristic respiratory epithelium or a metaplastic epithelium of stratified squamous type. This form of epithelial behavior called to mind the sequence described by Wolbach in the course of deprivation and restoration of vitamin A.[16-18] The second factor initiating reparative reaction was the deterioration of epithelial cells which followed calcification of mucus in the secretory vacuoles of goblet cells (Fig. 3). These cells, in the absence of any signs of diminished viability, inflammation, and undue calcification of subepithelial basement membranes or deeper stroma, were occasionally transformed into spherical, concentrically laminated, calcified crystalline structures. This form of primary epithelial calcification usually stimulated a regenerative reaction in which proliferation of basal cells led to atypical orientation of the new epithelium in relation to rigid calcified basement membranes. Ordinarily this activated the regional stroma which produced an entirely new structure with characteristics of the original basement membrane. The new membrane was interposed between the discontinuous calcified original basement membrane and the proliferating epithelium. As this occurred, the displaced calcified membrane became encapsulated by histiocytes or incorporated in the cytoplasm of multinucleated giant cells.

Despite the apparent interference of these changes with tracheobronchial function, little associated inflammation was provoked. A low-grade chronic tracheobronchitis, characterized principally by an

infiltration of plasma cells in the respiratory mucosa, was found in a few animals. This followed the most severe instances of stromal and epithelial calcification. It was never encountered in control animals and was regarded as a specific feature of hypervitaminosis D.

Not all parts of the tracheobronchial tree were equally affected by the calcific changes. The process developed more readily in the trachea and, as the disease became more severe, spread distally. Hence, in mild cases the principal changes were in the trachea. In moderately severe cases, the lesions were conspicuous as far distally as the terminal bronchi supported by cartilage. In the most severe cases, the process extended all the way into the walls of the alveolar ducts and alveoli. At times, the calcification of the terminal structures was very advanced, with involvement of pulmonary elastic tissue and the walls of interalveolar capillaries and pulmonary venules (Fig. 4). The alterations led to diminished elasticity with increased rigidity, relaxation, and fragility of alveolar structures. Thus, early stages of emphysema became conspicuous, and although peripheral pulmonary changes were usually associated with advanced tracheobronchial calcification, the relationship was not always encountered and was by no means quantitative. It was clear that factors which determined the locus and quantity of tracheobronchial calcification did not necessarily operate equally in determining the distribution and magnitude of calcification in alveolar walls and pulmonary vascular channels.

### *Alimentary Tract*

The upper alimentary tract was studied more carefully than the lower tract so that conclusions concerning changes distal to the duodenum were only tentative.

The esophagus showed no evidence of disease.

The stomach was a common site of severe calcification but only in special locations; namely, the part of the gastric wall concerned with support, nutrition, and the specific performance of acid secretion (Fig. 5). This part encircled the cardiac orifice and occupied the principal part of the fundus and greater curvature. The mucosa of the lesser curvature and the pyloric region contain few if any parietal cells which are generally held to be responsible for secretion of hydrochloric acid. The parts of the gastric wall which were calcified are therefore spatially and presumably functionally integrated. Calcium in the muscular wall was usually most conspicuous, and there was concurrent calcification of the mucosa and arterial system. Deposits of calcium in the mucosa

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usually appeared first in the *tunica propria* and basement membranes adjacent to the common junction of branches of the compound glands in the midmucosal regions. Occasionally, cells lining the glands were calcified, and at times calcified concretions lay in the lumens of glands. Later, stromal calcification also occurred in other locations, especially near the muscularis mucosae. In connection with the stromal deposits, calcified walls of small arterioles were conspicuous, and at the level of the muscularis mucosae and submucosa, calcification of walls of larger arterioles and small arteries was still more prominent. Walls of larger arteries deeper in the *tunica muscularis* and serosa were less severely calcified although calcium deposits in the internal elastic membrane and subjacent media were common. In these vessels, fibroelastic intimal proliferation was apparent, always overlying calcified or fragmented stretches of abnormal internal elastic membranes or subjacent media.

Calcium deposition in the *tunica muscularis* and the muscularis mucosae of the stomach occurred in a characteristic sequence and pattern. Major deposits lay in the cytoplasm of smooth muscle cells which seemed, initially at least, to be structurally normal. The smooth muscle cells were ordinarily affected in groups, and with increased calcification only the bare outlines of initial structure remained. In its place there were rows of curious calcified bodies which resembled strings of beads without recognizable origin in cytoplasmic structure (Fig. 6). Minor deposits of calcium appeared in tortuous curved structures which at times resembled fibrous or elastic elements and at other times minute canaliculi or autonomic nerve axons. Further study will be required for the identification of these calcified filaments, fibers and other structures.

The pattern of transmural calcium deposition in elective sites in the stomach disappeared with the transition of gastric mucosa to the type which secretes no acid. Indeed, the entire thickness of the gastric wall just beyond the level of mucosal transition was normal in all cases. In other words, all arteries, nerves, smooth muscle, mucosal glands and stroma in the non-acid-secreting part of the stomach were free from calcium deposition.

Immediately beyond the pyloric sphincter, which at times contained a few clusters of calcified smooth muscle cells, a different pattern of calcification was encountered. Here, the duodenal mucosa, *tunica muscularis* and muscularis mucosae were ordinarily spared while calcium deposits appeared conspicuously in the walls of small arteries and arterioles. Distal to the duodenum the only important calcium

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deposits were in the *tunica muscularis* of the ileum and especially the colon. The deposits varied greatly in amount and position. Mucosal and arteriolar calcification was indistinct or absent, except in the colon, in the reticulum of lymphoid follicles or in the basement membranes of interglandular surface epithelium. There was a peculiar concentration of calcium in and around ganglionic plexuses in the *tunica muscularis* of the colon. Other plexuses were uninvolved. Mucus-secreting goblet cells, commonly calcified in the respiratory mucosa, were unaffected throughout the ileum and colon.

### *Urinary Tract*

The kidney was also a common site of severe disturbance and was affected in all cases in which there was significant calcification in other tissues.[3,4,8] The renal calcification was confined principally to aggregates of functionally related units. For instance, nephrons were not involved equally or in a random manner. Those first affected were nearest the medulla, and from this region the process spread to involve the more peripheral nephrons but seldom reached those in subcapsular areas (Fig. 7). In connection with this curious wave of calcification there was a similar spread in the medullary tubular areas corresponding to the distribution of loops of Henle.

The sequence of changes in nephrons was also of interest. The epithelium of the convoluted tubules seemed most susceptible; the cells were frequently solidly impregnated with calcium often disposed in a spherical, concentrically laminated pseudo-crystalline fashion, occupying and expanding the original volume of the cytoplasm and nucleus. Intraluminal calcified protein casts were also encountered in these tubules. The basement membranes of the convoluted tubules had a conspicuous affinity for calcium so that at times they were more heavily calcified than the epithelial cells. This affinity was prominent beyond the limits of the convoluted tubules, especially in the stroma of Bowman's capsule. Less often, the subendothelial membrane of glomerular arterioles was affected.

No conspicuous calcification of tubular epithelium and basement membranes of the kidney appeared without calcification of the related arterial system. The large extrarenal arteries were least involved, although calcification of internal elastic membranes and subjacent patches of medial structure was usual. Where the extrarenal arteries branched to enter the cortex, near the corticomedullary junction, pathologic changes became more prominent. The walls of arteries and arterioles supplying the nephrons undergoing mineralization were fre-

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quently solidly impregnated with calcium so that mural structure was hardly recognizable (Fig. 15). The process of arterial calcification ordinarily extended in continuity to the glomerular tuft (Fig. 8). Involvement of the glomerular arteriolar plexuses was uncommon except when calcium was deposited in spherical masses scattered throughout the tuft in swollen glomerular endothelial cells. The postglomerular arterioles and venous channels were spared, except in the most severe instances of diffuse calcification. This was equally true of all arterial and venous systems connected with the nephrons of the peripheral half of the renal cortex.

The most remarkable feature of the renal lesions was their distribution. Of interest also, however, was the absence of expected signs of inflammation. Nor was there ever more than a trace of the reparative reaction one would anticipate in response to the observed magnitude and duration of renal damage. The disease was essentially indolent, progressive and degenerative.

The remainder of the urinary tract was not studied carefully, but ureters and renal pelves were often included in the sections. The ureters were always normal. The pelves ordinarily contained subepithelial deposits of calcium, occurring at intervals in the fibroelastic connective tissue and among bundles of smooth muscle cells. There was no inflammatory reaction preceding calcium deposition although the stromal fibers were often swollen and nodular. Following calcium deposition, there was in some instances a proliferation of histiocytes resembling the reaction encountered in similar calcified tissues in several other locations.

### *Vascular System*

Particular attention was given to a study of the vascular system.[2,5] The earliest evidence of hypervitaminosis D was in the proximal aorta and changes were always found here, whenever there were calcific deposits in other locations such as the tracheobronchial mucosa, gastric wall and kidneys. As the disease became more severe and prolonged, calcium deposits appeared in the midaorta, then in the distal aorta, and at about the same time, in various aortic branches.

Microscopically, the initial calcium deposits in the aorta were in and along the innermost elastic membranes and delicate intermembranous fibrils or matrix (Fig. 11). With increasing duration and severity of the disease, calcification increased in depth and magnitude. In advanced cases the inner third of the media of the proximal aorta was calcified in continuity, and there were discontinuous annular zones of calcification in the middle third of the media. The depth of pene-

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tration of calcification in continuity decreased slightly with increasing distance from the aortic valve but not in proportion to the decrease in thickness of the media. Hence, in advanced cases, the full thickness of the media of the distal aorta was calcified, while not more than the inner half of the media of the proximal aorta was similarly involved.

Each aortic branch had individual susceptibility to mineralization, and each had its own pattern of calcium deposition. In general, branches of similar size and structure had similar susceptibilities and patterns, but this was not an invariable rule. Without undue description of deviations, the trends in the different systems may be given as follows. As the elastic structure which dominated the composition of the upper aorta was gradually replaced by an increased amount of smooth muscle in the distal aorta and carotid, renal or iliac arteries, calcification of the internal elastic membrane became more conspicuous and local deposits of calcium appeared in and between the subjacent smooth muscle cells (Fig. 14). The deposits in the beginning were discontinuous and distributed in an annular manner (Fig. 12). As they increased in number and extent, they tended to fuse to form annular rings and to spread in the long axis of the media, eventually occupying it entirely. The process was especially conspicuous in the iliac and femoral arteries. A similar lesion but with less annular and axial discontinuity of calcification was common in the carotid, axillary and brachial arteries (Fig. 13).

Changes in the smaller and more peripheral branches of these arteries did not follow any uniform pattern which could be related to the dimension or structure of the vessel. For instance, the immediately extrinsic and intrinsic vessels of the cerebral vascular system were always normal. The main pulmonary artery and major branches occasionally contained discrete calcified lesions of the inner media, but the minor branches down to the level of the alveolar capillary network were usually normal. At the alveolar level, calcium deposition became conspicuous and extended in continuity to involve the media of vessels of the outflow venous system into the left atrium (Fig. 4). Arteries to special organs such as the submaxillary glands, kidney, spleen, thymus, duodenum, acid-secreting part of stomach and thyroid were often very severely affected, while those supplying the eye, testis, ileum, adrenal, pituitary and liver were spared from significant alteration. Arteries to skeletal muscle, pancreas, bone marrow and skin contained lesions to a variable degree among different animals and from place to place in the same animal. These general statements also pertain to arterioles and capillaries.

Veins, except those carrying blood from pulmonary alveolar spaces to the left atrium, were never electively involved, though venous channels in the kidneys, bone marrow and elsewhere were occasionally secondarily affected in connection with massive calcification of regional tissue.

Not only were there unexplained vagaries in localization of calcium in different arteries and arterial systems, but the patterns of reaction associated with the localization were equally variable. For instance, fibrous intimal proliferation was negligible in the proximal aorta. It increased in magnitude in the aorta with increasing distance from the aortic valve. It was maximal in the systemic arteries of large caliber which showed severe calcification and fragmentation of internal elastic membranes supported by medias composed largely of smooth muscle rather than layers of elastic lamellae. It was limited exclusively to areas covering abnormal internal elastic membranes and subjacent medial structures in most animals, and predominantly so in all animals. The fibrous intimal plaques formed sluggishly but at times within 6 weeks acquired a thickness equal to that of the arterial wall (Fig. 14). In smaller arteries, the intimal proliferation was less conspicuous so that in arterioles, despite extensive transmural calcification, intimal proliferation was scarcely recognizable, except in the presence of active or healed arteritis (Fig. 16).

The occurrence of arteritis was another unexplained variable. The evidence indicated that the arteritis was related to exceedingly high dosage levels and perhaps to acute intercurrent infection. Suffice it to say that arteritis of the type occurring in animals with hypervitaminosis D was never encountered in the control animals, many of which also died of acute intercurrent infections. Whatever the eventual explanation, the arteritis and periarteritis had no specific connection with the degenerative calcifying disease of arteries in general. There was good evidence that it was connected with the occurrence of calcified deposits in distal arterial systems lying within muscle and concerned principally with the nutrition of cardiac and skeletal muscle (Figs. 1, 16). Seldom was arteritis or periarteritis encountered elsewhere and then only in isolated vessels and never in the conspicuous generalized form noted in the muscles.

Not only was the anatomic distribution of the arteritis a matter of considerable significance, but the pattern of inflammation of arterial walls and perivascular tissues was equally interesting. The most severe forms were in the nature of an indolent panarteritis, which resembled reactions occurring in periarteritis nodosa, lupus erythematosus, rheumatic fever, and occasionally rheumatoid arthritis. In less severe cases,

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the signs of inflammation were principally in the collagenous adventitial tissues. These signs varied from a mild nodose swelling of the fibrils to a more pronounced response characterized by aggregates of histiocytes, neutrophils and lymphocytes in and around foci of degeneration of perivascular interstitial tissues. At times, especially in the myocardium, several persons who have studied these sections have remarked the similarity of the lesions to Aschoff bodies. Similarity was all that could be claimed, however. The lesions were entirely unlike the random inflammatory foci encountered occasionally in the myocardium of rabbits in the control series.[1,8]

### *Muscular Systems*

The preceding descriptions have disclosed that the muscular tissues of the body were usually affected. There was no evidence that this involvement was secondary to alterations of arteries, although arterial lesions customarily accompanied muscular abnormalities. Smooth muscle was more generally affected than cardiac or skeletal muscle. Changes in smooth muscle of the media of systemic arterial and pulmonary venous systems, the *tunica muscularis* of the alimentary tract and the tracheobronchial tree, and the mucosa of the renal pelvis have already been described. Similar changes were less common in such other locations as the corium of the skin and septa of the spleen. Though successive stages of development of the lesions in smooth muscle were similar in most locations, this was not true of all locations, and there were wide differences in the susceptibility of various smooth muscle cells. In general, cardiac and skeletal muscle were less susceptible than smooth muscle, whereas skeletal muscle in most locations was less susceptible than cardiac muscle. In some instances, manifestations of inflammation and cellular degeneration preceded the microscopic signs of calcification of muscle. In other instances, however, the intracellular deposition of calcium seemed to occur in muscle which showed no definite evidence of inflammation or degeneration (Fig. 6). Whether these occurred or not seemed to be related to the rapidity of development and severity of the disease. At times, the stromal elements around smooth muscle cells were affected before there was conspicuous calcification of the cells. At other times, the cells were initially altered, and the stromal elements resisted calcification. This resistance of the stroma was generally apparent when cardiac muscle was undergoing calcification, but less so when calcium was being deposited in skeletal muscle cells. In the latter instance, the sarcolemma of some fibers was calcified before the cells had acquired much calcium.

The dominance of this disease in many tissues concerned with motion is well illustrated by the remarkable changes which occurred in the skeletal system.[12,18] The first effects occurred early and were characterized by a resorption of bone, a decrease in the prominence of osteoblasts, and an increased prominence of osteoclasts (Fig. 9). These changes were more conspicuous in cortical than trabecular structures. A significant amount of pathologic calcification of the viscera did not occur unless these alterations were demonstrable. The development of abnormal calcium deposits in the viscera was also accompanied or followed by abnormal basophilic deposits of osteoid tissue in the skeleton. These deposits occurred not only in locations notable for the degree of osseous resorption but also in the bone marrow, along the margins of persistent trabecular and cortical bone (Fig. 10). Though there was some local increase in stroma which either preceded or accompanied the abnormal massive osteoid deposits, any close resemblance to normal sequences of osteoblastic orientation, osteoid production or calcium deposition was lacking. The osteoid tissue seemed to engulf old stroma, reticulum cells and other structures in a spreading wave beginning at the margin of pre-existing bone and progressively obliterated the adjacent bone marrow. When this process ceased, the customary form of normal eosinophilic osteoid tissue with incorporated osteocytes began to appear as local islands in the midst of the widespread basophilic osteoid deposits. This indicated onset of repair and, with passage of time, the deposits were largely replaced by new bone. There resulted an osteosclerosis characterized by excessive reformation of bone along lines which did not reproduce the initial or normal pattern of bone growth. The final result was a deformed skeletal structure, usually with a porous cortex. This was accompanied by a thick layer of periosteal new bone, especially excessive at the margins of some articular surfaces, and an excess of trabecular bone which had encroached upon an abnormal bone marrow (Fig. 10). As a rule, the response of the bone marrow to calcification and osteogenesis was fairly consistent in the areas which remained free from fibrosis. The marrow which had not been replaced by fibrous tissue, abnormal osteoid tissue, or new bone, was depleted of fat cells and was densely cellular. Hematopoietic elements varied considerably in their relative proportions and stages of maturation in different animals. The commonest abnormalities were maturation arrest and diminished numbers of megakaryocytes associated with an increase of cells resembling megaloblasts or plasma cells. Conspicuous cytologic changes in the marrow were

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usually accompanied by calcification of the media of blood vessels which appeared to belong to the arterial system. As yet, no connection between the changes in hematopoietic elements and the severity of the disorder in other parts of the body has been established though a correlation with gastric disease is strongly suspected.

The spleen was usually not severely disturbed. The earliest deposits of calcium occurred in the interiors of the septa. Here, fibroelastic tissue and smooth muscle were electively calcified, but the bulk of the calcium was deposited in collagen. There was no consistent evidence of any inflammatory or degenerative change prior to calcification, although collagen fibrils often were swollen and irregular in outline. In some instances the arterial system was more heavily calcified than the trabecular structure. Here, the main splenic artery and its major branches regularly showed calcification with fragmentation of the internal elastic membrane overlying foci of medial calcium deposition. Fibrous intimal proliferation was seldom conspicuous but, when found, always was superimposed on degeneration of the vascular wall. As the splenic arterial branches entered the spleen and decreased progressively in diameter, transmural calcification became increasingly conspicuous so that the walls of many follicular arterioles were uniformly calcified. Nor did the impregnation of vascular structure cease here, for in some cases it continued into the walls of the sinusoids and outlined the reticular framework of lymphoid follicles.

### *Endocrine and Other Glands*

The principal calcium deposits in endocrine glands were in the thyroid and thymus. In the thyroid the small arteries were usually severely affected in animals with advanced generalized disease. The vascular process was associated with atrophic changes in glandular epithelium and diminution in the amount of colloid. This in turn was related to variable calcium deposits in basement membranes of follicles and interfollicular stroma.

The thymus gland showed conspicuous atrophy in severely diseased malnourished animals. Calcium deposits were restricted principally to Hassall's corpuscles although occasionally there were deposits in the media of small arteries and arterioles.

The pituitary never contained calcium deposits. There were unexplained variations in the ratios of cell types in the anterior lobe. The parathyroid glands were normal in size and in histologic characteristics. The adrenal glands were resistant to calcification with deposits occurring only in the most severe cases. These appeared only in occasional

swollen endothelial cells of the vascular sinuses in the cortex. Large vessels were spared.

The testes were seldom affected, except insofar as the illness led to reduced spermatogenesis. There were occasional calcified concretions in tubules and insignificant calcium deposits in the media of large arteries leading to the testis; these were minor late manifestations of severe generalized disease.

Other glandular structures had their individual changes. The liver was never affected, even though the arterial branches at the hilus showed the same types of calcium deposition as other branches of the celiac axis. Intrahepatic vessels were free from lesions.

The large branches of the splenic artery to the pancreas were affected to about the same extent as the arteries to the spleen. The vascular changes decreased with diminishing size of the arteries so that in contrast to splenic arterioles the arterioles in the pancreas were usually normal. In occasional lobules of the pancreas of severely affected animals, the process extended into the arterioles, and the extension was accompanied by atrophy of acinar cells with calcification of the delicate basement membranes of glands. The pancreatic islets were not affected.

The arteries and arterioles supplying the submaxillary glands were among the most susceptible peripheral vascular structures. The walls of these vessels were often densely calcified. The process varied from one lobule to another. Accompanying the most severe arteriolar lesions, there was a tendency for other degenerative and calcific changes to occur; these were epithelial atrophy, calcification of inspissated secretion in the acini of glands or small ducts, and heavy impregnation of basement membranes with calcium. The sequence of these changes was not clearly defined, but the evidence indicated that vascular and epithelial changes preceded changes in the intervening stroma.

### *Central Nervous System and Eye*

The eye was regularly spared except for small deposits of calcium in the sclera. This comment excludes any consideration of the lens because it was not examined microscopically. Retinal arteries were never calcified.

There were no deposits of calcium in the brain or spinal cord. This was a consistent observation and applied to all structures ordinarily associated anatomically with the brain and spinal cord. The level to which calcified deposits in the carotid, vertebral and spinal arteries extended from their points of origin has not been determined, but no vascular alteration has yet been found in the intracranial or intraspinal

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divisions of these vessels. Furthermore, the vascular system within the confines of the pia mater and gray or white matter was always spared from calcification even around foci indicative of chronic intercurrent meningo-encephalitis which was encountered in a few animals of our current stock.

### *Skin and Adipose Tissue*

The skin showed changes which need not be described in detail. Beneath the epithelium and at a slightly deeper level in the corium, the lesions resembled those occurring in fibroelastic tissues elsewhere. In connection with these alterations in their advanced form, there was mild calcification of the tributary arteriolar and precapillary walls. Other histologic features resembled the early modifications in human cutaneous fibroelastic tissue designated "senile elastosis." In the deeper tissues, lesions were insignificant except where short stretches of fascia were lightly calcified and where skeletal muscle showed degeneration of the type described elsewhere.

Adipose tissue in most locations was unaffected by the disorder. However, in the retroperitoneal tissues, especially around the larger arteries and adrenals, severe atrophy of fat cells was encountered, usually accompanied by a deposition of calcium. The principal deposits were either adjacent to or in the cytoplasmic membranes of fat cells. No massive deposits were encountered in the interior of fat cells.

## Discussion

A major problem in analysis of the pathogenesis of many generalized diseases is an inability to explain the vagaries of distribution of the anatomic or functional manifestations. In one patient the manifestations of a disease may be referable to a single system or some part thereof. In another, the manifestations of the same disease may be referable to more than one system or more than one part of any system. In still others, the manifestations may be dissociated so that the expected quantitative relations between the anatomic and functional changes are not found. Concepts which guide thinking in these matters have no solid foundation in structural or functional pathology.

It was our belief that an experimental study of an easily controlled metabolic derangement which produced widespread structural changes of a simple degenerative nature rather than a complex inflammatory reaction might lead to formulation of more suitable concepts.[19] Wolbach demonstrated with well-planned experiments and great interpretive insight that the use of deficiencies and excesses of vitamins was an elegant method for approaching problems of this kind.[16-18] After surveying this subject, it was decided that a systematic experimental

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study of hypervitaminosis D might be helpful for our purposes, and that this eventually might be compared with experimental hyperparathyroidism.[11,21,22]

The widespread changes disclosed by this study may be summarized as follows. First, degenerative changes with calcium deposition occurred in many organs and tissues. Second, the pattern of distribution of the degenerative changes was not specifically related to any common physical, chemical, or other characteristic of the affected elementary tissues or their combinations. Third, the sequences in development of these changes were not the same everywhere but were determined in part by unknown factors characteristic of the affected organ or tissue. Finally, the pattern and sequences of degeneration occurred in a reproducible fashion which could not have been predicted from a knowledge of factors which ordinarily determine the local characteristics of generalized disease processes.[16]

The widespread distribution of pathologic changes was largely dependent upon the amount of irradiated ergosterol given, the interval between doses, and the duration of the experiment. The data indicated that a sufficient quantity of the vitamin would produce minimal changes if it were given in a single dose or in a series of small daily doses over a period of several days. Maximal subacute changes due to the same quantity of the vitamin occurred when it was given in equal divided doses at intervals of 2 or 3 days. The best regime for obtaining maximal, chronic, slowly progressive changes has not been established, but good results followed the interposition of prolonged rest periods between brief dosage schedules designed to produce bursts of maximal active changes.

The pattern of distribution of pathologic alterations was constant under a given regime but varied somewhat with variation of the experimental conditions. In general, however, the earliest evidence of degeneration appeared in a particular location in each affected tissue or organ. Then, the process spread to involve other tissues or the same tissue in a succession of locations, each of which was resistant to change until the antecedent pattern of degeneration was set. Each affected type of tissue in each affected location in each affected organ had a definite level of susceptibility to the degenerative changes. This curious order of susceptibility to degeneration with calcification led to the conclusion that each type of cell or tissue in a functionally integrated system had a characteristic degeneration-calcification potential and that the level of the potential varied among different integrated systems. Hence, the succession of tissue alterations might be regarded as a result of the operation of four mechanisms. The first mechanism

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raised the calcification potential of the tissue. The second raised the calcifying potential of the environmental fluids. The third was concerned with adaptation, and the fourth with restoration.

It is generally accepted that the best way to increase the calcification potential of a cell or tissue which does not normally calcify is to reduce its viability without bringing about rapid structural disintegration.[11] In the present experiments, it was clear that there was a reduction in viability of certain cells and stromal elements. It was not clear whether the reduction preceded or followed the deposition of calcium salts.[8] If reduction in viability preceded calcification, there was at this stage little evidence of customary findings of lessened viability. In other words, the earliest evidence of modification of stroma or cells did not definitely precede evidence of calcification in many locations. Furthermore, in most pathologic conditions, the reduction of viability of stroma and cells ordinarily initiates a sequence of inflammatory and regenerative reaction before calcium deposition becomes conspicuous. In the present study, this was not encountered as an early reaction in any location, except perhaps in certain muscular tissues, and then only in connection either with intolerably high dosage or intercurrent infection. However, under these conditions, conspicuous inflammatory reactions did not occur prior to degenerative calcifying changes, and the reactions were restricted principally to the arterial systems in cardiac and skeletal muscle. Usually, the reactions were confined to the media and adventitia of arteries, but in the severe cases there was a spread into neighboring muscle. The distribution of the inflammatory reaction, when it occurred, coincided with the distribution of the degenerative calcifying changes which developed without signs of inflammation in muscle of other experimental animals. From this it may be inferred that some factor increased the degeneration-calcification potential in all instances, but an inflammatory reaction was not elicited except when it was excessive or when other factors, perhaps related to intercurrent infection, were introduced. In any event we must admit the possibility of a more complex form of local tissue potential which might be called an inflammation-degeneration-calcification potential. Thus, under the same systemic conditions local factors may induce various combinations of inflammation, degeneration and calcification to occur at the same time in different organs or in the same tissue types in different organs.

The second mechanism seemed to be related to the composition of oxygenated or arterial blood and to special units of tissue integrated together in the performance of some particular function. For instance, emphasis has often been placed upon the deposition of calcium in tis-

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sues concerned with acid secretion.[8,9,11] The explanation has been that the secretion of acid led to a local alkalosis which in turn enhanced the likelihood of local precipitation of calcium phosphate and carbonate. Inasmuch as arterial blood is ordinarily more alkaline than venous blood, the view may be taken that through diffusion, systemic arterial walls may be more alkaline than venous walls, the reverse being true in the pulmonary system. The view may also be taken that the alkalinity of oxygenated systemic arterial blood decreases progressively with increasing distance from the alveolar capillaries and venules. Hence, if the interstitial fluids of the vascular wall reflect the local alkalinity of the blood, the deposition of calcium and associated degenerative changes of constituent tissues might be expected to fall off progressively in the direction of flow of the arterial blood. The microscopic observations disclosed that this was not always so. In a further analysis of this matter, the lung, kidney and stomach may be considered separately as the three principal acid-secreting organs.

Theoretically, it might be predicted that the region of maximal alkalinity in the lung would be in connection with the blood in the postalveolar pulmonary venules, and that maximal degenerative calcifying changes would occur in the walls of these vessels. In general, this was the case (Fig. 4). There were negligible lesions in the pulmonary arterial system, and the conspicuous changes were initially found in the walls of interalveolar capillaries and adjacent interalveolar stroma. Later, the venules and small pulmonary veins were affected. Insofar as the respiratory passages are concerned, if we accept free diffusion of gases into tissues, the level of maximum alkalinity would be in the upper trachea (Fig. 3). Hence, it might be predicted that the changes would be more conspicuous here than in the terminal bronchi. In general, this was found. The tracheal structures showed the earliest changes, and as a rule calcification along the respiratory passages decreased progressively in identical tissue types in identical locations with increasing distance from the larynx. In a consideration of this rule, however, other factors have to be considered. First, the lesions around the circumference of any respiratory passage were not uniform at a given level. The earliest changes were either in goblet cells of the epithelium or in the subjacent stroma. With increasing time and severity of the disease, the changes spread circumferentially and also in a very specific way in depth. The circumferential spread finally led to involvement of the entire basement membrane zone and an increasing span of epithelium. The spread in depth tended to skip the loose collagenous tissues of the mucosa and to appear in the walls of mucosal vessels nearest the subepithelial zone of calcification, the smooth

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muscle in the neighborhood, and the part of bronchial cartilages contiguous to the maximal mucosal changes. Thus, it seemed that the distribution, the sequences, and the magnitude of lesions were determined by the operation of local influences, as follows: alkalinity of environmental gases and fluids, type of tissue, type of cell, and the locally integrated functions of susceptible types of tissues or cells.

An analysis of alterations in the stomach may also be attempted in terms of relative alkalinity of parts of an acid-secreting organ. One might postulate that maximal alkalinity would be in relation to the venous blood flowing from the acid-secreting mucosa and that maximal calcification would occur in the tissues supporting the acid-secreting glands and in the walls of vessels leading from these tissues. This was not found even though, when mucosal changes did occur, they were restricted to the acid-secreting mucosa and to the *tunica propria* or cells of glands responsible for this function. Such changes, however, were inconspicuous in the early stages and often followed the development of prominent changes in the walls of arteries, the *tunica muscularis*, and muscularis mucosae (Fig. 5). Veins or venules were seldom affected. It might be assumed, therefore, that if relative alkalinity governed the distribution of the lesions in the stomach, it would have to operate in a curious way throughout the gastric wall. Consequently, it seemed that an inquiry should be made into the role of locally integrated functions of susceptible types of tissues or cells. It was apparent that the calcification was not a disorder of the acid-secreting gastric mucosa alone but a disturbance of the full thickness of the gastric wall concerned with acid secretion. For present purposes, the acid-secreting part of the stomach should be considered transmurally as a functional unit, separate and distinct, pathologically, from the remainder of the stomach. We have no explanation as to why the arterial system, the *tunica muscularis*, the muscularis mucosae and, to a lesser degree, the mucosa of only this part of the stomach were so severely affected by this degenerative calcifying disease. It offered a puzzling example of localization of pathologic changes in all susceptible tissue types in a functionally integrated system in a special location. The remainder of the intestinal tract offered other problems in this connection; namely, the variable pattern of involvement of the *tunica muscularis* at different levels, the variable resistance of different mucosal types to the disorder, and the restriction of severe arteriolar disease to the duodenal and, to a lesser extent, colonic segment of the intestinal tract.

Changes of the type found in the kidney have also been attributed to a local alkalosis, secondary to secretion of acids by the kidney.[10,11] It might be predicted therefore that changes would occur in that part

of the kidney just distal to the postabsorptive tubulovascular structure or in some special region concerned with selective absorption of alkaline elements or selective secretion of acidic elements. Actually, the earliest alterations occurred in the cells of the proximal convoluted tubules, soon thereafter in the basement membranes of these tubules, and somewhat later in the arterial supply to the affected nephron rather than the venous return from the nephron (Fig. 7). Thereafter, the arterial tree was usually progressively involved with increasing severity (Figs. 8, 15). It was concluded that within the limits of present knowledge of renal function, other factors than local alkalinity determined the distribution and sequence of the changes. As in the instance of the lungs and stomach, these factors were concerned with the interrelationships between susceptible tissue types in a functionally integrated system in a given location. The spread of changes in the kidney demonstrated this very well. In the early stages only a scattering of total nephrons as complete units showed lesions, but these were the nephrons with short arterial connections close to the medullocortical junction. As more lesions developed, the intervening nephrons with similar arterial connections were affected. With increasing time and severity of the disease, there was a spread of the changes distally toward the capsule, but seldom did the animal live long enough to show much alteration in the nephrons of the peripheral third of the cortex. As cortical spread developed, there was a similar spread of changes in an ever-broadening medullary zone within which the medullary loops of the successively affected nephrons were presumably located. These sequences are presumably related to the distribution of functional load rather than of a specific secretory function among a system of nephrons.

The preceding comments have touched upon local factors such as alkalinity, type of tissue, type of cell and locally integrated functions of susceptible tissues or cells. Muscle cells were among the least resistant, the order of decreasing susceptibility being smooth, cardiac, and skeletal muscle. Furthermore, the most readily affected component of these cells was the contractile protein, especially the "A" disk. Among the stromal elements, the severest lesions appeared in elastic tissue, basement membranes, the matrix of cartilage and the sarcolemmal investiture of muscle cells. Cellular and stromal elements were not equally susceptible in all locations. Hence, the development of this systemic metabolic disorder did not result in a generalized modification of a given element, and this is analagous to the effects of certain "toxins."[23] On the contrary, it led to conspicuous modifications of these elements in specific locations without changes in identical struc-

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tures in other locations. The extent to which this selectivity may be attributed to unrecognized differences in elements assumed to be identical, remains an intriguing problem. Certainly there are good reasons for believing that the composition of structures such as smooth muscle cells, collagen, elastic tissue, basement membranes and cartilaginous matrices is not the same everywhere. By the same token, the functional burden to which these elements are subjected is not the same everywhere.

The third mechanism was concerned with adaptation. Three adaptive activities deserve mention: the intimal proliferative reactions in arteries; the excessive production of atypical osteoid matrix following extensive resorption of bone; and the regression of the disease despite continuation of the same dosage regime which produced it. The discussion of these and other less obvious adaptive reactions awaits the completion of more prolonged experiments.

The fourth mechanism was concerned with restoration, principally the resorption or elimination of abnormal mineralized tissue, and the regeneration of tissues to replace those attacked by the disease. The salient feature of this mechanism was its indolence. In the respiratory mucosa, desquamation of calcified goblet cells and regeneration of basal cells to replace them were sluggish processes. At times, the regenerative sequences took a metaplastic trend so that the degenerated epithelial layer was replaced by one or more layers of stratified squamous epithelium. Wherever this occurred, there were local defects in the basement membrane and chronic inflammation in the subjacent mucosa. The mineralized basement membranes also tended to persist, being very slowly resorbed (Fig. 3). With increasing mineralization, there was increased fragility of these structures. Fractures developed and discontinuities thereby created seemed to stimulate local proliferation and accumulation of histiocytes. These commonly formed multinucleated giant cells which slowly resorbed the mineralized stromal structure, often encapsulating it completely. As this proceeded, the mineralized basement membrane seemed to migrate to a deeper level, and a regenerated stromal support appeared as a new structure between it and the respiratory epithelium. Similar mechanisms of encapsulation and resorption were encountered as far distally as the alveolar ducts but were seldom detected in connection with the calcified components of alveolar walls or pulmonary vascular channels. Alveolar walls seemed to break down spontaneously with the production of emphysema, but it was not clear that these mechanisms participated in the rupture (Fig. 4).

The behavior of the mesenchyme adjacent to abnormally mineralized

cartilages along respiratory passages was also interesting. Intense mineralization was usually conspicuous on the mucosal side of the cartilage. The perichondrium became less distinct, and the margin of the calcified matrix acquired a moth-eaten appearance. Capillaries occasionally invaded the marginal lacunae, and in some instances there was active formation of new cartilaginous matrix by proliferating chondrocytes. These activities resembled those which normally occur at provisional zones of endochondral bone formation. The overall result here, however, was the slow resorption of the heavily calcified bronchial and tracheal cartilages without osteogenesis.

Resorption and regeneration were still more sluggish in the kidney. Calcified tubulovascular components of the nephron seemed to endure without resorption or regeneration for at least several weeks. Evidence of regeneration of tubular epithelial cells of affected nephrons, compensatory hyperplasia of tubules of spared nephrons, interstitial fibrosis, inflammation, arteritis, glomerulosclerosis or other responses were never significant. The principal reaction occurred in the precortical and large cortical arteries. Here, there was intimal proliferation, excited less by degeneration and calcification of the media than by discontinuities due to fractures of calcified internal elastic membranes (Fig. 15). Whatever lesser reactions occurred in the subepithelial stroma of the renal pelvis were similar in most respects to those described in connection with the basement membranes of the respiratory tract.

Resorption and regeneration in relation to the acid-secreting part of the gastric wall were also very sluggish. The mucosal structures were not very responsive to the degenerative changes. The intimal reactions in the arterial tree were more active than in other organ systems, and the proliferative reactions also extended further into the smaller arterioles. The muscularis mucosae and the *tunica muscularis* showed the most conspicuous evidence of resorption and regeneration. In both locations, the degenerated calcified smooth muscle and intervening stroma often stimulated local histiocytic and giant cell reactions. These cells assisted in the resorptive process. Also, at times, there were many large pale elongated immature elements which appeared to be regenerating smooth muscle cells. In no case, however, was there significant leukocytic infiltration, local vascularizing reaction or fibrosis.

The complexities of resorption and regeneration in the skeletal system were difficult to interpret. Initially, the resorption of bone was accelerated, the number of osteoclasts was increased, and the number

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of osteoblasts was decreased (Fig. 9). A curious proliferative process followed, resulting in the formation of a large amount of abnormal osteoid matrix beneath the periosteum and in the marrow around the residual cortical and trabecular bone (Fig. 10).[12,18] Though this matrix may be called "osteoid," it was more fibrillar, less homogeneous and much more heavily stained with hematoxylin than normal osteoid tissue. Furthermore, there was no relation between the voluminous deposits of matrix and any particular array of cells which resembled osteoblasts. The tissue looked more like collagen which had as much affinity for hematoxylin as any of the extra-osseous calcified stromal or cellular elements. With onset of repair, normal eosinophilic osteoid tissue and bone appeared in the midst of this voluminous basophilic fibrillary material which was resorbed. It was conspicuous only when extra-osseous calcium deposition had essentially ceased or in the period following termination of ergosterol administration. The prompt and rapid formation of bone was more pronounced in connection with the peritrabecular matrix and in the subperiosteal regions adjacent to the margins of articular cartilages. This led to a deformed osseous framework with depleted porous cortical bone, an excess of periosteal new bone, an excess of endosteal bone, and a coarse dense trabecular structure displacing the marrow. The final result had some resemblance to osteosclerosis of a pagetoid type with myelofibrosis (Fig. 10). The development of atypical hematopoietic elements as these changes encroached upon the bone marrow is beyond the limits of this discussion.

Finally, it was clear that a moderate dosage regime was most effective in the first few weeks. As the regime was continued, the expected progression of pathologic changes failed to occur, and evidence of the disease slowly disappeared. This was attributed to the activation of obscure mechanisms which provided increasing tolerance, resistance or immunity to the action of excessive vitamin D. In the light of certain degenerative calcifying human diseases, an inquiry into the nature of these adaptive and restorative mechanisms would seem to be of first importance.

## Summary

A microscopic study of the evolution of hypervitaminosis D in rabbits disclosed generalized pathologic sequences which were due to partly reversible inflammatory, degenerative and mineralizing processes. The participation of these processes in the pathogenesis of the disease in a given location was governed principally by the level and duration of dosage with the vitamin. Administration of the vitamin in amounts just sufficient to produce pathologic changes in 2 or 3 weeks

led to mineralization of certain tissues which do not normally calcify. Under these conditions the deposition of calcium occurred without significant preliminary local structural modifications attributable to inflammatory or degenerative processes. When somewhat larger doses of the vitamin were used, abnormal mineralization of tissues was often preceded and accompanied by structural changes of a degenerative type. In order to excite significant early inflammatory reactions, still larger doses of the vitamin and perhaps other factors were required. These reactions occurred only in cardiac and skeletal muscle. They were localized to the walls of arteries, periarterial tissues and adjacent muscle, in which there were signs of progression of degeneration and mineralization.

Studies of restorative phases of the disorder disclosed evidence of reversibility and resistance to progression of these processes. The inflammatory reactions in muscle subsided, and mild indolent reparative reactions appeared in many degenerated mineralized tissues. Furthermore, additional degenerative changes seemed to progress very slowly, if at all, while, at least in some locations, the process of mineralization was slowly reversed even though the dosage was maintained. The reversal was characterized by the resorption of abnormally calcified matrices. At times, this occurred spontaneously, but as a rule the resorption was associated either with mobilization of macrophages and giant cells or penetration of the calcium deposits by vascularized stroma. The signs of reversal were usually preceded or accompanied by resumption of osteogenesis in the abnormal osteoid matrices in bone.

The same type of tissue or cell in different locations was not equally affected by the inflammatory-degenerative-mineralization mechanisms, presumably because of a difference not only in the composition of tissue gases and fluids from place to place but also in the susceptibility of a particular tissue in different locations. The latter was governed primarily by participation of a cell or tissue in a functionally integrated and spatially related system which had in one or more of its parts a high calcification potential.

The designation of function as adding to or detracting from the inflammatory-degenerative-calcification potential of a given structure led to a better understanding of patterns of the disease, especially in the respiratory tract, kidney, stomach, muscles and arteries. It may also assist in the future analysis of the reasons for the resemblance between certain structural changes in this experimental disease and those encountered in some presumably unrelated human disorders which are indolent, fundamentally degenerative, and ordinarily attributed to ill-defined metabolic derangements of advancing age.

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Among these, senile osteoporosis, hypertrophic arthritis, pulmonary emphysema and arteriosclerosis deserve more than fleeting consideration, so long as it is recognized that identity of structural change does not imply identity of pathogenesis.

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## LEGENDS FOR FIGURES

FIG. 1. Multiple, focal, inflammatory-degenerative-calcification changes in the myocardium of a rabbit given 600,000 units of viosterol in 2 weeks. The inflammatory reaction is located principally in and around the walls of small arteries and arterioles which in turn are surrounded by cardiac muscle showing degeneration with early calcification. Hematoxylin and eosin stain. × 200.

FIG. 2. Massive calcification of cardiac muscle in a rabbit given 1,200,000 units of viosterol in 7 weeks. The degenerated calcified muscle cells have multiple transverse fractures through which proliferating stromal elements have grown. The isolated calcified fragments of cells have undergone partial resorption. There is no inflammatory reaction. Hematoxylin and eosin stain. × 150.

FIG. 3. The tracheal mucosa of a rabbit given 1,200,000 units of viosterol in 7 weeks. Intra-epithelial calcification is in the form of concentrically laminated pseudocrystals which seem to develop exclusively in the goblet cells. The subepithelial calcification is concentrated in the darkly stained fragmented basement membrane. Note the absence of inflammation. Hematoxylin and eosin stain. × 500.

FIG. 4. A peripheral field of the lung of a rabbit given 1,200,000 units of viosterol in 6 weeks. Hematoxylin has a strong affinity for calcified tissue, demonstrated here as deeply-stained black segments of an emphysematous alveolar wall and the entire thickness of the wall of a small pulmonary vein. These changes in alveolar and venous walls regularly occurred together and were independent of inflammation. Hematoxylin and eosin stain. × 500.

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FIG. 5. A cross-section of the wall of a part of the stomach concerned with secretion of hydrochloric acid. The rabbit from which this section was made was given 1,600,000 units of viosterol in 14 weeks. Hematoxylin has an affinity for calcified tissues, shown as irregular small dark areas in the mucosa, in the walls of submucosal arteries, in the bundles of smooth muscle of the inner half of the *tunica muscularis* and in the wall of a small serosal gastric artery. Hematoxylin and eosin stain. × 40.

FIG. 6. A high-power photomicrograph of one of the small darkly stained calcified areas in the *tunica muscularis* of the wall of the stomach shown in Figure 5, showing degenerated smooth muscle cells in the midst of granules and filaments of calcified protoplasm demonstrated by its strong affinity for hematoxylin. The small calcified granules are in the cytoplasm of the muscle cells. The tortuous calcified filaments are external to smooth muscle cells and seem to consist largely of interstitial fibrous or reticular elements. Hematoxylin and eosin stain. × 600.

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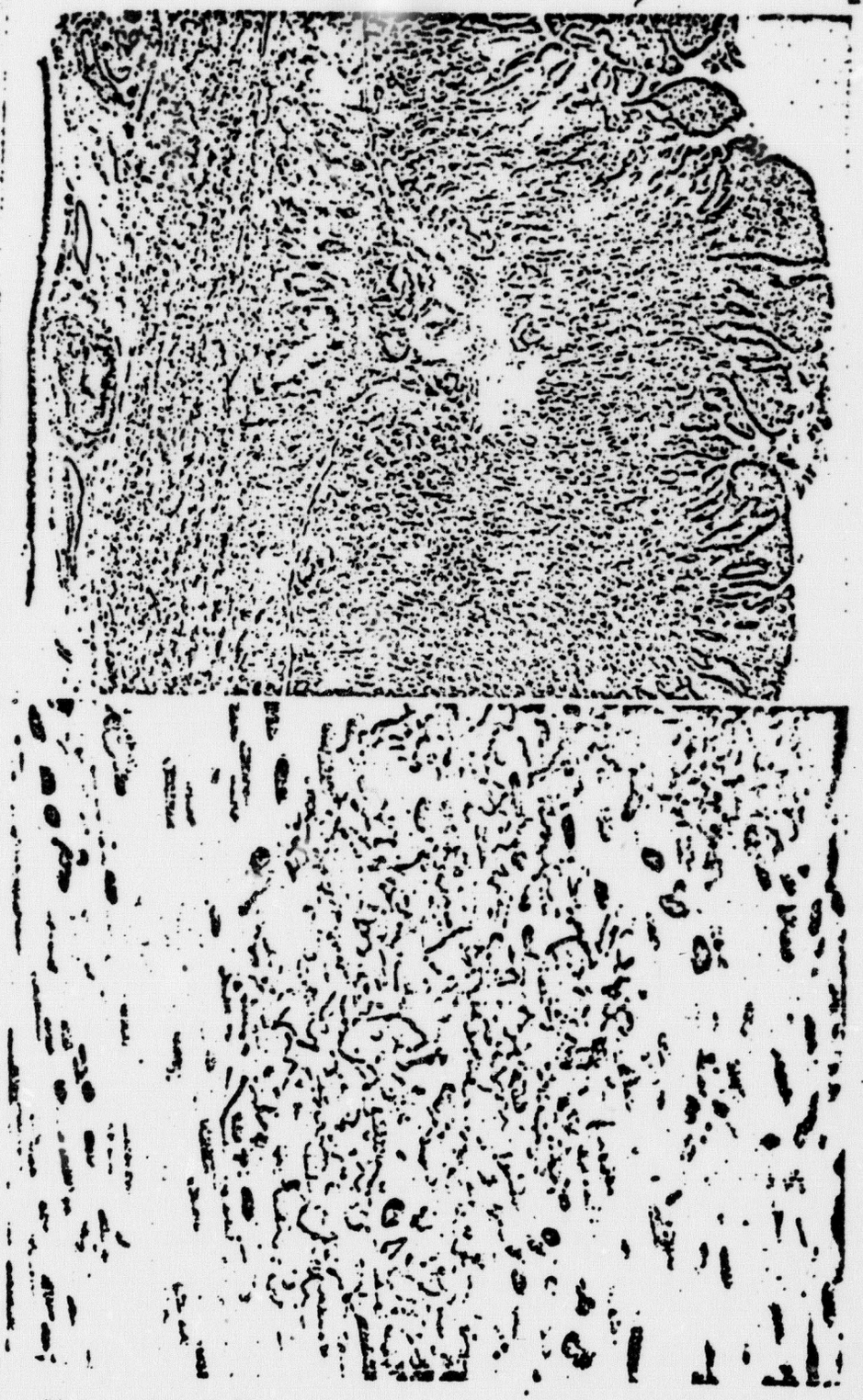

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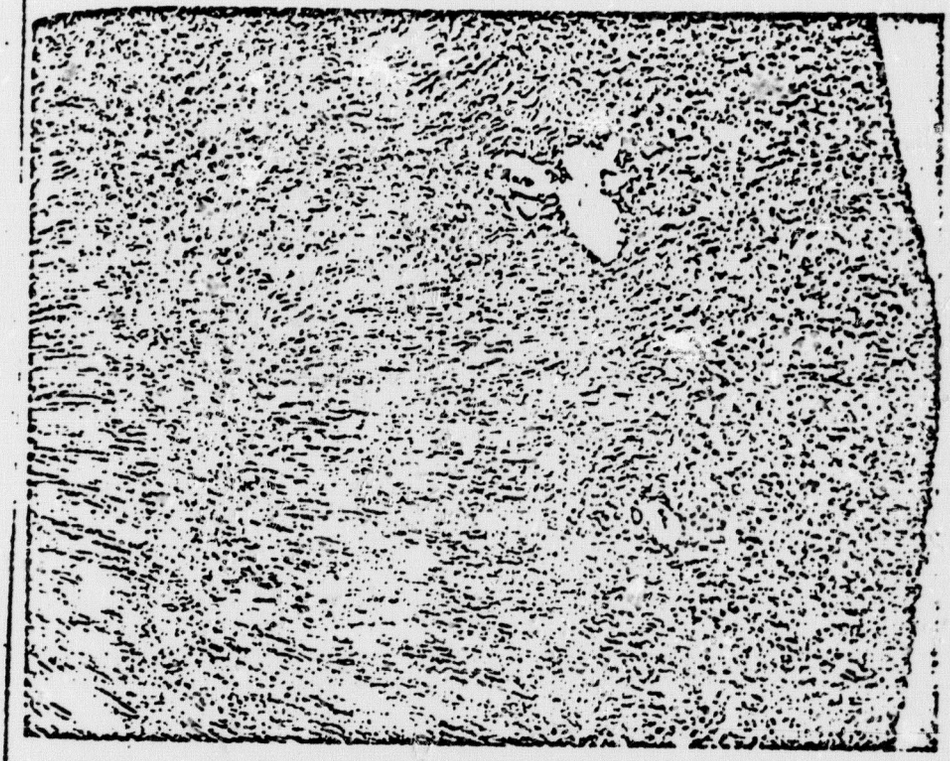
FIG. 7. The cortex and medulla of a kidney from a rabbit given 1,000,000 units of viosterol in 5 weeks. Six weeks later the animal was sacrificed. The loss of normal structural detail is apparent in the inner half of the cortex and in a narrow transverse zone in the middle of the medulla. The small dark spots represent calcified structures in these 2 locations. The intervening lightly stained areas which are more conspicuous in the cortex are places where proliferating connective tissue has replaced degenerated tubulovascular units of nephrons. This represents an early stage of resorption of mineralized tissue with repair and regeneration. Inflammation is negligible in the kidney at all times during the development or regression of the disease. Hematoxylin and eosin stain. × 23.

FIG. 8. A field in the inner third of the cortex of a kidney of a rabbit given 800,000 units of viosterol in 4 weeks. This shows early calcification of glomerular structure with minimal associated alterations in tubular structure. The calcified elements have an affinity for hematoxylin. There is a tendency for calcium to accumulate in isolated glomerular loops. In one glomerulus the accumulation is in continuity with the calcified wall of the arteriole entering the glomerulus. Hematoxylin and eosin stain. × 220.



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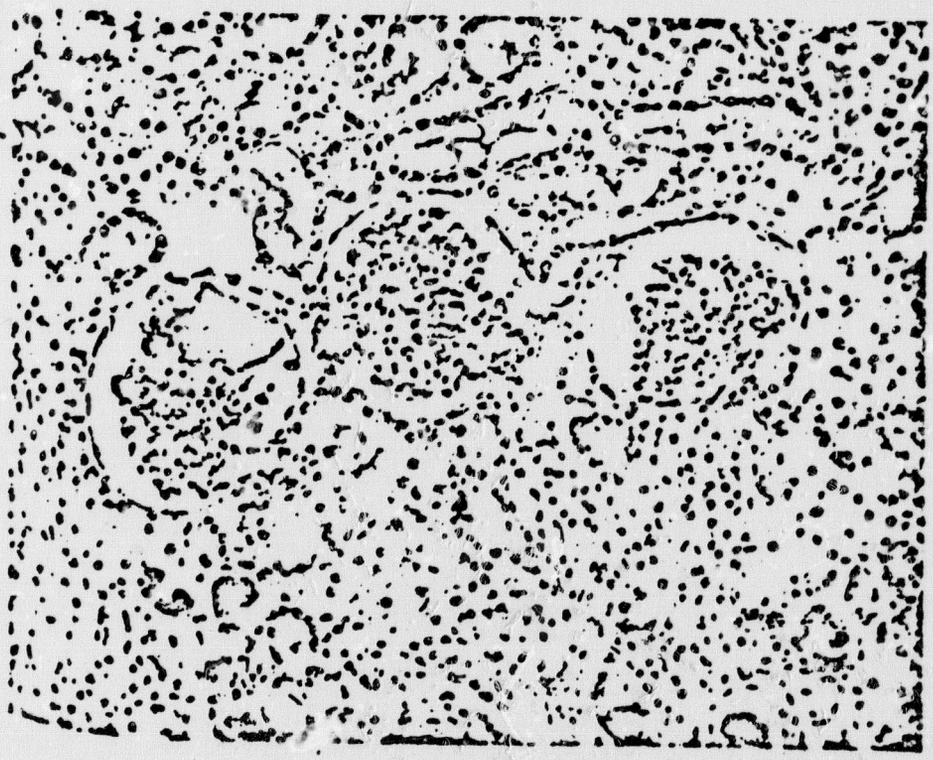

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FIG. 9. A longitudinal section of a rib from a rabbit given 1,200,000 units of viosterol in 4 weeks, showing widespread resorption of bone with conspicuous porosity of cortical bone, fibrosis of the marrow, and early subperiosteal deposition of osteoid tissue. The changes are characteristic of the disorder between the third and fifth weeks. After about the fifth week, the changes illustrated in Figure 10 become increasingly dominant. Hematoxylin and eosin stain. × 60.

FIG. 10. A longitudinal section of the vertebral column of a rabbit given 1,200,000 units of viosterol in 12 weeks. The resorption of bone, typical of early stages of the disease (see Fig. 9), has led to partial collapse of a vertebral body which is at this later stage undergoing an osteosclerotic pagetoid change. This is characterized by excessive deposition of osteoid tissue which has a conspicuous dark color due to its affinity for hematoxylin. Much of this abnormal osteoid tissue has been converted to bone, producing a dense trabecular structure which has seriously encroached upon the marrow. Also, note the proliferative changes which have produced "spurs" of new bone at the margins of the intervertebral disks. Hematoxylin and eosin stain. × 10.

FIG. 11. A cross-section of the wall of the thoracic aorta of a rabbit given 600,000 units of viosterol in 2 weeks. The inner third of the elastic tissue framework, stained deeply with hematoxylin, is uniformly impregnated with calcium. Note the absence of any inflammatory reaction though only a trace of residual cellular structure remains between the calcified elastic lamellae. Hematoxylin and eosin stain. × 250.

FIG. 12. A cross-section of an iliac artery of a rabbit given 1,000,000 units of viosterol in 5 weeks. The segmental darkly stained areas represent subintimal bands of calcific deposits in the inner half of the media. These discontinuous deposits tend to spread in all directions until they occupy the entire media. Meanwhile, there is a reactive proliferation of the intima which in time tends, as shown, to be equal in thickness to the part of the subjacent media inactivated by calcification. Hematoxylin and eosin stain. × 30.

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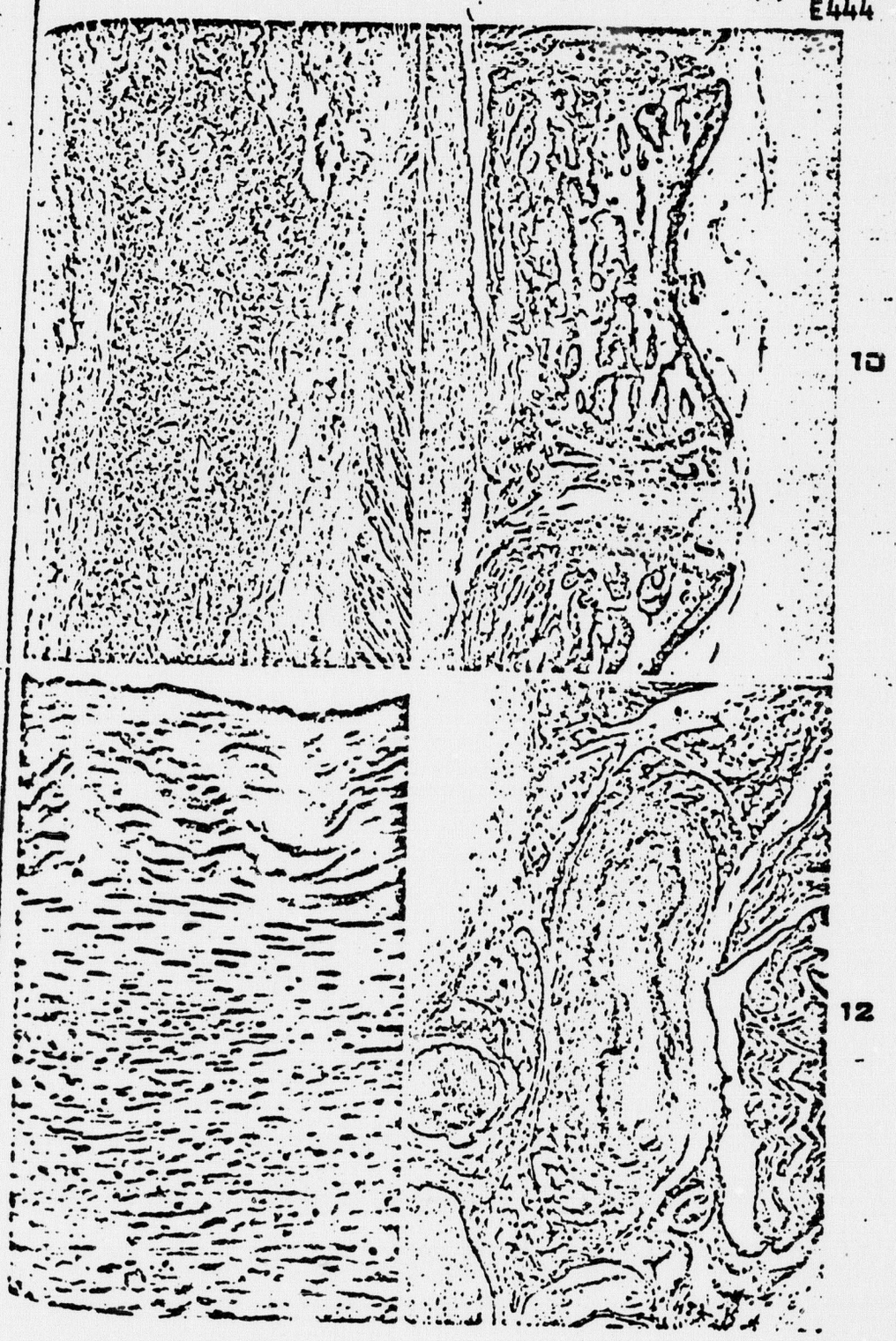

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FIG. 13. A cross-section of a carotid artery of a rabbit given 1,000,000 units of viosterol in 15 weeks. From the lumen outwards 3 distinct zones are shown. They are of almost equal thickness. The inner zone is composed of proliferating fibrocellular intimal tissue. The middle zone, deeply stained with hematoxylin, is the inner half of the media which has been uniformly impregnated with calcium. The outermost zone is the external half of the media which has been unaffected by the disease. Hematoxylin and eosin stain. × 32.

FIG. 14. A pancreatic artery of a rabbit given 1,600,000 units of viosterol in [illegible] weeks. The darkly-stained material in the vascular wall is calcified tissue with a strong affinity for hematoxylin. The deposits of calcium involve most of the internal elastic membrane and a modest amount of the media subjacent to the calcified parts of the internal elastic membrane. Three short stretches of the internal elastic membrane and adjacent media are normal. The loose-textured fibrocellular tissue internal to the calcific deposits is proliferating intima. Note that intimal proliferation did not occur over the 3 stretches of internal elastic membrane which were unaffected by the calcific disease. Hematoxylin and eosin stain. × 225.

FIG. 15. A small artery and adjacent arteriole in the renal cortex of a rabbit given 1,500,000 units of viosterol in 2 weeks. The walls of these vessels are heavily calcified as indicated by the strong affinity of the media for hematoxylin. Swollen intimal cells with their nuclei projected away from the calcified media toward the lumen of the larger artery represent the earliest intimal reaction to degenerative calcifying medial disease. Hematoxylin and eosin stain. × 600.

FIG. 16. A tiny arteriole in skeletal muscle of a rabbit given 1,200,000 units of viosterol in 7 weeks. The media of the arteriole, stained deeply with hematoxylin, is uniformly calcified. The swelling of the intima has reduced the size of the lumen. In the adventitia there are a few inflammatory cells representing a mild form of periarteritis often found in cardiac and skeletal muscle of rabbits dying of pneumonia during the course of a high-dosage viosterol regime. Hematoxylin and eosin stain. × 500.

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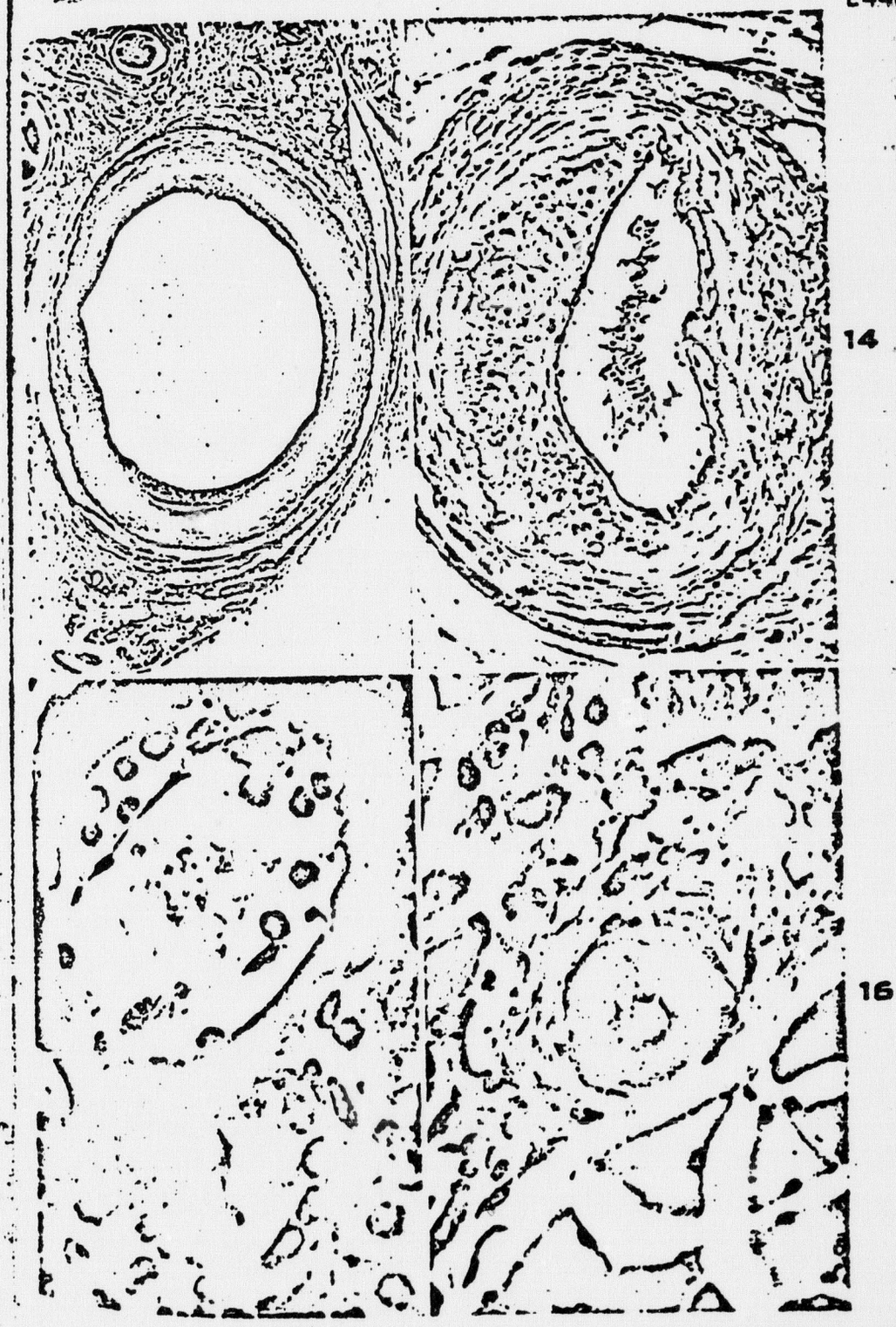

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Таким образом, при лечении строфантином больных с недостаточностью кровообращения параллельно клиническому улучшению наблюдается уменьшение протромбинового индекса и повышение свертываемости крови. В случаях, когда, несмотря на терапию строфантином, явления отеков, стойко держался застой в легких и оставались не исчезали отеки, стойко держался застой в легких и оставались не исчезали

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## THE INFLUENCE OF DIGITALIS, STROPHANTHIN AND MERCUSAL ON THE THROMBOGENIC PROPERTIES OF THE BLOOD IN PATIENTS WITH CARDIAC INSUFFICIENCY

*L. N. Yakovlev*

Summary

The paper presents investigations on the blood coagulation, prothrombin index, bleeding time and thrombocyte count carried out in 65 patients suffering from rheumatic heart defect and atherosclerotic cardiosclerosis with circulatory insufficiency of different stages, who were subjected to digitalis or strophanthin treatment. When the effect of treatment was good there was observed in almost 50% of patients an increase of the prothrombin index and shortening of the blood coagulation time which, however, were within normal values. These changes are associated, apparently, with the improved function of the liver.

Mercusal did not produce any noticable changes in the blood coagulation indices.

## О ГИПЕРВИТАМИНОЗЕ D И ИДИОПАТИЧЕСКОЙ ГИПЕРКАЛЬЦИЕМИИ У ДЕТЕЙ РАННЕГО ВОЗРАСТА

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Как известно, витамин D ненапизается в организме, и чрезмерное и длительное его применение может вызвать токсические явления. В большинстве руководств указывается, что токсическая доза витамина D превышает в несколько раз терапевтическую дозу и поэтому практически D-гипервитаминоз у детей не наблюдается. На основании наблюдений, проведенных в Тартуской городской детской клинической больнице за последние 2 года мы с этим не можем согласиться. Приведем пример.

Кай Р., 1 года 2 месяцев. Мать давала ребенку по поводу рахита в течение 4 месяцев рыбий жир, получая в среднем по 62 500 единиц в день. Клинические явления гипервитаминоза возникли у ребенка уже через 3-4 месяца, когда ребенок получил в общей сложности 6 млн. единиц витамина D. Ребенок прожил вместе с родителями в Сибири около 2 лет, где получал витамин D в том же количестве. Привезен в Тарту 2 месяца назад.

При приеме в больницу ребенок был очень истощен, кожа бледная, с сероватым оттенком, на щеках и ягодицах — фолликулярные высыпания. Подкожная клетчатка почти не ощущалась. Подкожный жировой слой отсутствует. Ребенок не может самостоятельно сидеть, не держится на ногах. Отмечается выраженная мышечная гипотония. Мышцы дряблые, сухие. Кожа сухая, шелушащаяся. Ребенок раздражителен, плохо спит. Аппетит очень плохой, ест неохотно. Рвота неукротимая, неоднократная. Стул 3-4 раза в день, кашицеобразный, иногда с примесью слизи. Живот вздут, печень выступает из-под реберной дуги на 3 см по Кивричу. Селезенка не пальпируется. Моча без патологических изменений. Содержание общего белка в сыворотке крови колеблется в пределах 7,0-8,0 г%, белковых фракций — в норме. Содержание кальция в сыворотке крови колеблется от 10 до 15 мг% (норма 9-11 мг%), в моче обнаруживались следы белка, единичные эритроциты и в большом количестве — кристаллы оксалата кальция. Креатинин и мочевина крови в пределах нормы. Реакция Вассермана отрицательная. Рентгенологически: легкие без изменений, сердце нормальной конфигурации, размеры его несколько увеличены. Тени сердца и легких в пределах возрастной нормы. Содержание витамина D в крови 20 мг%, РОЭ колеблется в пределах от 10 до 15 в час. Кровь на белковые фракции не исследовалась. Ребенок был помещен в больницу с диагнозом: рахит, тяжелая степень, подострое течение, осложненный гипервитаминозом D. Назначено лечение: 1% раствор хлористого кальция по 1 чайной ложке 3 раза в день, 10% раствор глюконата кальция по 1 чайной ложке 3 раза в день, 10

Таким образом, только десятикратное превышение суточной терапевтической дозы витамина D в течение 4 месяцев вызвало у ребенка тяжелый D-гипервитаминоз.

По данным В. А. Власова и В. К. Столяровой, параллелизма между количеством введенного витамина D и явлениями интоксикации не наблюдалось.

За последние годы появились данные об особой нозологической единице у детей раннего возраста, так называемой идиопатической гиперкальциемии (R. Lightwood, J. M. P. Dawson и др., K. G. Lowe и др., D. G. Greery и D. W. Neill и др., I. O. Forfar и др.). При этом заболевании у детей наблюдается гиперкальциемия (12—20 мг%), в то время как содержание неорганических фосфатов и щелочной фосфатазы в сыворотке крови нормальное. Щелочный резерв крови бывает обычно нормальным, содержание гамма$_2$-глобулинов повышено. Многие авторы наблюдали гиперхолестеринемию. Такое состояние наблюдалось у детей при обычной или несколько повышенной дозировке витамина D. Клинически выражен синдром гиперкальциемии, и поэтому картина болезни сходна с D-гипервитаминозом. При тяжелых формах болезни можно констатировать задержку роста и умственного развития ребенка, а также явления общего висцерального кальциноза. Тяжелые формы этого заболевания могут оканчиваться как летально, так и выздоровлением (Th. Stapleton).

При так называемой идиопатической гиперкальциемии резорбция кальция в кишечнике повышена. Обычно всасывается 35% кальция коровьего молока, при применении витамина D — до 50%, а при идиопатической гиперкальциемии — 60% (H. G. Morgan и др.). Причины возникновения этого заболевания еще полностью не выяснены. Существует мнение, что одной из наиболее частых причин является индивидуальная повышенная чувствительность к витамину D, так как при приеме этого витамина болезнь ухудшается, при прекращении приема улучшается. Развитию идиопатической гиперкальциемии способствует применение пищи с большим содержанием кальция, поэтому она встречается преимущественно у искусственно вскармливаемых детей, так как содержание кальция в коровьем молоке в 4½ раза больше, чем в грудном. Развитию гиперкальциемии способствует также применение пищи со щелочным остатком и употребление лекарственных препаратов, вызывающих ощелачивание.

Нижеприводимые наблюдения показывают, насколько различной может быть реакция организма на введение витамина D.

Хельга К., 6 месяцев. Мать по собственной инициативе давала ребенку с наступлением весенний раствор витамина D в течение 4 месяцев, всего 2,5 млн. единиц, т. е. в среднем 20 833 единицы в день. Через 2½ месяца ребенок стал беспокойным, появился понос. Позднее появилась рвота, запор. За последний месяц потеря в весе 700 г. Девочка стала вялой, появилась субфебрильная температура. Начиная с четырехмесячного возраста ребенок на смешанном вскармливании, а с 5½ месяцев — на искусственном.

При приеме в больницу имелись следующие симптомы: ребенок вялый, очень худой сместся, кожа сухая, тургор тканей понижен, гипотрофия первой степени, авитаминоз отсутствует, язык обложен, рвота почти после каждого приема пищи, запор, субфебрилитет. Реакция Сульковича положительная, количество кальция в сыворотке крови 15,5 мг%, РОЭ 35 мм в час. Моча без патологических изменений. После прекращения приема витамина D настроение ребенка постепенно стало улучшаться, прекратилась рвота, появилось нарастание в весе. Содержание кальция в крови нормализовалось через месяц, а РОЭ — через 2 месяца после прекращения приема витамина D.

Таким образом, только двукратное превышение дозы витамина D в течение 4 месяцев вызвало у ребенка, находившегося на смешанном вскармливании, состояние гиперкальциемии.

[illegible] давала ребенку

витамина D (в 1 мл 50 000 единиц), следовательно 40 000 единиц ежедневно. За 4 месяца ребенку было дано 2¼ флакона масляного раствора витамина D, что составляет 3 375 000 единиц. Никаких клинических явлений D-гипервитаминоза у ребенка не наблюдалось. Содержание кальция в сыворотке крови 11,4 мг%. Только на рентгенограмме можно было отметить в эпифизах трубчатых костей более интенсивное обызвествление.

В данном случае даже десятикратное повышение дозы витамина D в течение 4 месяцев не вызывало у 10-месячного ребенка клинических явлений D-гипервитаминоза.

Приведенные примеры показывают, насколько различной может быть реакция организма на введение витамина D. Это зависит, по всей вероятности, от индивидуальных особенностей организма, от состояния повышенной чувствительности или резистентности организма.

Вышеизложенные литературные и клинические данные показывают, что явления гиперкальциемии могут возникнуть и при более низкой дозировке витамина D. Если при профилактике или лечении рахита витамином D у ребенка наблюдается потеря аппетита без всяких видимых причин, появляется апатия, падение веса, то следует немедленно прекратить дачу витамина D. Кроме того, необходимо выяснить содержание кальция в крови и сделать рентгенограммы с эпифизов трубчатых костей.

Лечение D-гипервитаминоза и так называемой идиопатической гиперкальциемии должно быть направлено на уменьшение гиперкальциемии. Нами применяются следующие мероприятия. Немедленно прекращается прием витамина D и препаратов кальция, а также ультрафиолетовое облучение. Пища должна быть бедной кальцием (менее 300 мг в день), но в то же время достаточно калорийной и содержать животные белки в достаточном количестве для восстановления веса больного. Грудным детям лучше всего давать женское молоко, содержание кальция в котором равно 25 мг%; в коровьем же молоке кальция содержится 115 мг%, в 4½ раза больше. Для уменьшения количества кальция в коровьем молоке рекомендуется применять поглощающие смолы (Е. Н. Хохол и др., A. V. Ferguson, C. K. McGowen, Г. Андерсон и др., H. G. Morgan, Th. Stapleton и др.). В настоящее время на нашей кафедре (Х. Ю. Куус) разработана методика по получению коровьего молока, в котором количество кальция при помощи смолы КУ-1 уменьшено в 3—4 раза.

Не следует применять продукты, богатые кальцием — сыр, яичный желток, рыбные консервы, икру, фасоль, цветную капусту, шпинат, миндаль. Для питья и приготовления пищи можно рекомендовать дистиллированную воду, так как в обычной воде содержится около 5—20 мг% кальция. Больному назначается обильное питье для предотвращения развития нефрокальциноза.

Для уменьшения всасывания кальция рекомендуется применять кортизон (Th. Stapleton, H. G. Morgan), который в противоположность действию витамина D задерживает всасывание кальция в кишечнике. Для улучшения обмена веществ рекомендуется давать больному в достаточном количестве регулирующие обмен веществ витамины (A, $B_1$, $B_2$, PP).

Прописывая детям препараты витамина D, врач обязан назначить точную дозу на курс лечения и предупредить родителей о вредном его действии при излишнем применении. Для точной дозировки следует при выписке рецепта на витамин D выписывать и пипетку.

Большие дозы витамина A задерживают развитие D-гипервитаминоза (С. Н. Мацко), поэтому при лечении рахита наряду с большими дозами витамина D целесообразно применять одновременно витамин A

## Выводы

1. Явления D-гипервитаминоза могут развиться даже при незначительных передозировках витамина D.

2. Чувствительность детей к витамину D может быть индивидуально весьма различной.

3. Во время лечения витамином D следует внимательно следить за ребенком и при появлении первых симптомов гиперкальцемии прекращать прием витамина D.

4. При назначении детям препаратов витамина D необходимо предупреждать родителей об опасности передозирования.

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## D HYPERVITAMINOSIS AND IDIOPATHIC HYPERCALCINATION IN CHILDREN OF EARLY CHILDHOOD

*L. M. Keres*

**Summary**

The analysis of clinical cases shows that even a two-fold increase of vitamin D given for a long period of time may cause a severe D hypervitaminosis. The individual sensitivity of vitamin D in children is quite different. Pertinent literature data presents a special nosological entity in children of early age — the so-called idiopathic hypercalcination. One of the most frequent causes of this disease is the individual elevated sensitivity to vitamin D. Hence, when instituting vitamin D treatment, special attention should be paid to the child's condition, and upon appearance of the first symptoms of hypercalcination the administration of vitamin D must be stopped.

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# К ВОПРОСУ ОБ ОСЛОЖНЕНИЯХ ПРИ ПЕРВИЧНОМ РАКЕ ЛЕГКОГО

*А. В. ГРИГОРЯН, В. С. ЖДАНОВ*

Из кафедры общей хирургии (зав. — проф. В. И. Стручков) лечебного факультета I Московского ордена Ленина медицинского института имени И. М. Сеченова и патолого-анатомического отделения (зав. — действительный член АМН СССР проф. Н. В. Давидовский) больницы имени Медсантруда (главный врач А. П. Тимофеева)

Диагностика рака легких до сих пор еще остается трудной. Это заболевание нередко не распознается даже в специальных учреждениях, иногда же имеет место гипердиагностика рака легкого.

Трудности диагностики связаны прежде всего с тем, что рак легких у огромного большинства больных сопровождается хроническим воспалительным процессом. Он-то нередко и определяет клиническую картину. Вместе с тем хронические воспалительные процессы в легких не всегда являются осложнениями рака, нередко они предшествуют развитию его (С. С. Вайль, И. К. Есипова, В. И. Стручков, Д. Ф. Скрипниченко, Л. Т. Хазанова и др.). Важно, однако, подчеркнуть, что атипические изменения эпителия, которые можно условно назвать предраковыми, встречаются нередко у лиц сравнительно молодого возраста — 30 лет (А. В. Григорян, В. С. Жданов, Е. В. Рыжков). Это свидетельствует о том, что для развития рака на почве хро-

нических воспалительных изменений требуется, по-видимому, много лет. У этих больных при последующем развитии рака отмечается длительный «легочный анамнез», свидетельствующий о наличии хронических воспалительных процессов в легких. При развитии рака легкого без предшествующих хронических воспалительных процессов эти процессы осложняют течение рака, чаще всего незадолго до смерти, и имеют, как правило, более или менее ограниченный характер. Отсюда ясно, что хорошо собранный анамнез у значительной части больных помогает уточнить характер воспалительного процесса в том отношении, является ли он первичным или вторичным по отношению к развитию опухоли.

Приводим два наблюдения.

Больной Г., 55 лет, поступил в больницу имени Медсантруда 25/III 1946 г. с жалобами на кашель с мокротой, боли в грудной клетке, больше слева, на общую слабость, высокую температуру.

Считает себя больным с 1941 г., когда после перенесенного гриппа появились боли в левой половине грудной клетки, кашель с мокротой. Лечился амбулаторно по поводу левосторонней пневмонии. Состояние больного улучшилось, продолжал прежнюю работу старшего инспектора. Однако через 6 месяцев состояние вновь ухудшилось: боли в грудной клетке, кашель с мокротой, температура повысилась до 38,5°. Указанные явления врачами трактовались как результат обострения хронического неспецифического воспалительного процесса левого легкого. С 1941 по 1943 г. больной был многократно госпитализирован в различные лечебные учреждения. Состояние его прогрессивно ухудшалось: нарастала общая слабость, усилились боли в грудной клетке, увеличилось количество мокроты (до 300 мл за сутки), временами с кровью, температура держалась в пределах 37,5—38,5°. В декабре 1947 г. при очередной рентгеноскопии грудной клетки было высказано подозрение на рак левого легкого.

При поступлении: состояние больного крайне тяжелое. Резкая бледность кожных покровов и видимых слизистых. Грудная клетка цилиндрической формы. При аускультации сухие и влажные хрипы в левой половине грудной клетки, а также в нижнем отделе правой половины грудной клетки. Пульс 85 ударов в минуту, слабого наполнения, ритмичный. Тоны сердца глухие. Артериальное давление 110/60 мм ртутного столба. Язык влажный, обложен белым налетом. Печень выступает на 3 поперечных пальца из-под реберной дуги, плотна на ощупь. Пальпация этой области болезненна.

При рентгеноскопии и рентгенографии выявлена медиастинальная форма рака левого легкого. Множественные абсцессы нижней доли правого легкого.

24/IV 1948 г. больной умер.

Патологоанатомическое исследование: в левом стволовом бронхе на расстоянии 3—4 см от места разветвления располагается опухоль, закупоривающая просвет бронха и прорастающая его стенку. Опухоль прорастает также и ткань легкого, преимущественно у ворот. Опухоль растет вдоль бронхов в виде тяжей. Некоторые бронхи расширены. В нижней доле очаги уплотнения серовато-желтого цвета. На плевре небольшие белые опухолевые узлы. В нижней доле правого легкого картина хронического неспецифического воспалительного процесса (пневмосклероз, абсцессы). Микроскопическое исследование: обнаружена картина бронхогенного плоскоклеточного рака левого легкого. Опухоль почти полностью закрывает просвет бронха и прорастает его стенку и окружающую легочную ткань. Кроме того, обнаружена картина неравномерно выраженного пневмосклероза, хронический бронхит, деструктивные бронхоэктазы и отдельные абсцессы как в левом, так и в правом легком.

У другого больного хронический неспецифический процесс вверху был обнаружен одновременно с опухолью.

Больной Х., 50 лет, поступил в больницу имени Медсантруда 5/II 1955 г. с жалобами на боль в правой половине грудной клетки, кашель и незначительное кровохарканье в виде отдельных плевков. Больным себя считает в течение 3 недель, когда впервые кровохарканье в виде отдельных плевков, появились боли в правой половине грудной клетки.

При клиническом и рентгенологическом обследовании был установлен диагноз рак правого легкого с сегментарным ателектазом верхней доли. 7/III 1955 г. операция — пульмонэктомия справа (проф. В. Н. Стручков). Гладкое послеоперационное течение.

Патологоанатомическое исследование: доставлено правое легкое. В просвете верхнедолевого бронха располагается опухоль, обтурирующая просвет его. Просвет нижнего и среднего долевого бронхов свободен. Бронхи, вплоть до мелких, расширены, просвет их заполнен густой гноевидной массой. Макроскопически обнаружена картина плоскоклеточного бронхогенного рака. В верхней доле перибронхиальный

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# ON HYPERVITAMINOSIS D AND IDIOPATHIC HYPERCALCEMIA IN YOUNG CHILDREN

Sovetskaya Meditsina (Soviet Medicine), Vol 23, Moscow, June 1959, pages 35-38.

L. M. Keres
Candidate of the medical sciences

As is known, vitamin D is accumulated in the organism, and its excessive and prolonged use may cause toxic phenomena.

The majority of pharmacology textbooks point out that a toxic dose of vitamin D exceeds by several hundred or a thousand times the therapeutic dose and that, as a consequence, hypervitaminosis D is practically never observed in children. Because of observations made in Tartu City Children's Clinic Hospital during recent years, we cannot agree with this statement. Here is an example.

Kay R. is 14 months old. Over a 4-month period, the mother administered to the child, because of the onset of rickets, a spirituous solution of vitamin D, in all -- 7.5 million units, or an average of 62,500 units daily. Clinical symptoms of vitaminosis appeared during the third month, after the child had been given, in the aggregate, 6 million units of vitamin D. The child lost her appetite and there were manifestations of constipation, apathy, and a subfebrile condition. Emesis was rarely observed. The child lost 2,100 grams of weight during the last two months.

Before her admission to the hospital, the little girl had been apathetic, at times capricious. Nor had she wanted to play or stand. Noted was the complete absence of appetite, intense constipation, exicosis (eksikoz), unusual skin dryness, and in the evenings a subfebrile temperature. The Sul'kovich urine reaction was clearly positive; in the blood serum, the quantity of inorganic calcium was 20 milligrams %. The erythrocyte sedimentation reaction ranged from 10 to 14 millimeters per hour according to Panchenko's method. Observed in the urine were traces of protein and the usual unit leukocytes; but at times a large quantity of leukocytes were encountered, as well as erythrocytes in a greatly augmented viewing field. Arterial pressure rose to 110/90 millimeters on the mercury column. Following the discontinuation of vitamin D, pathologic elements were observed in



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the urine for a month, the amount of calcium in the blood was raised within 1.5 months, subfebrile temperature continued for 2 months, and an accelerated erythrocyte sedimentation reaction was noted for 2.5 months.

In this manner, a more tenfold increase in the daily therapeutic dosage of vitamin D over a four-month period caused a grave case of hypervitaminosis D in the child.

According to the data of V. A. Vlasov and V. K. Stolyarova, no connection was observed between the quantity of introduced vitamin D and intoxication phenomena.

Appearing in recent years have been data on a special nosological unit in young children, the so-called idiopathic hypercalcemia (R. Lightwood, J. M. P. Dawson, and others; K. G. Lowe and others; D. G. Greory and D. W. Neill and others; I. O. Forfar and others). During this illness, children are observed to be afflicted with hypercalcemia (12-20 milligrams %), although, at the same time, the content of inorganic phosphates and alkaline phosphatases in the blood serum are normal. The alkaline reserves of the blood are usually normal and the content of gamma$_2$ globulins is increased. Many researchers have observed hypercholesterinemia. Such a condition has been noted in children during the usual or a somewhat increased dose of vitamin D. The hypercalcemia syndrome is clinically pronounced and, therefore, the picture of the disease is similar to hypervitaminosis D. During grave forms of the disease, a child's visceral calcinosis may be observed. Grave forms of this disease may either prove fatal or be overcome (Th. Stapleton).

During so-called idiopathic hypercalcemia, the resorption of calcium in the intestine is increased. Usually 35% of the calcium in cow's milk is absorbed; when vitamin D is administered, up to 50% is absorbed; and with hypercalcemia, up to 60% (H. G. Morgan, et al.). The reasons for the appearance of this disease are not yet clear. There is an opinion that one of the most frequent causes is an individual's increased sensitivity to vitamin D, since the administration of this vitamin causes the illness to worsen, and its discontinuation results in an improvement. Contributing to the development of idiopathic hypercalcemia is the ingestion of food with a large calcium content. Because of this, it is primarily encountered in nonbreast-fed infants, for the calcium content of cow's milk is 4.5 times higher than that from a mother's breast. Also contributing to the development of hypercalcemia is the use of food with alkaline surpluses and the application of medical preparations causing alkalization.

The following observations demonstrate how differently an organism can react to the introduction of vitamin D.

2) Khel'gi K. is six months old. The mother, on her own initiative, treated the child for a flourishing case of rickets with a buttery solution of vitamin D over a 4-month period -- in all 2.5 million units, or an average of 20,833 units daily. Within 2.5 months, the infant became restless and lost her appetite. This was followed by emesis and constipation. During the last month, she lost 700 grams of weight. The female infant became

torpid and had a subfebrile temperature. Beginning on the infant's fourth month, she was given a mixed feeding and at 5.5 months, she was given an artificial feeding.

When admitted to the hospital, she had the following symptoms: the infant was torpid, laughed rarely, and had a dry skin; tissue turgor was reduced; first-degree hypotrophy was present; there was a lack of appetite; the tongue was coated; the ingestion of food was almost always followed by emesis; and constipation and a subfebrile condition were observed. The Sul'kovich reaction was positive; the calcium content of blood serum was 15.5 milligrams %. The erythrocyte sedimentation reaction was 35 millimeters per hour. The urine manifested no pathological changes. Following the discontinuation of vitamin D, the attitude of the infant gradually began to improve, and her weight increased. The calcium content of the blood returned to the normal level within a month, and the erythrocyte sedimentation reaction within two months after the discontinuation of vitamin D.

Thus, a mere twofold increase in the dose of vitamin D over a four-month period caused a hypercalcemic condition in the child who was on a mixed feeding.

3)

Val'deko K. was ten months old. During the last 4 months, because of a slight case of rickets, the mother administered regularly, twice daily, 24 drops (12 drops each time) of a buttery solution of vitamin D (1.050 million units) amounting to 40,000 units daily. During the 4-month period, the infant was given 2.25 flasks of the buttery solution of vitamin D, which totaled 3.375 million units. The infant manifested no clinical symptoms of hypervitaminosis D. The calcium content of blood serum was 11.4 milligrams %. Only by roentgenogram was it possible to observe a more extensive calcification in the epiphysis of the tubular bones.

In this case, not even a tenfold increase in the dose of vitamin D over a four-month period caused clinical symptoms of hypervitaminosis to appear in the child.

The above-mentioned illustrations demonstrate how differently an organism can react to the introduction of vitamin D. This reaction depends, in all probability, on the specific characteristics of an organism, the state of heightened sensitivity or resistance of an organism.

The literature and clinical data presented above show that hypercalcemic phenomena may appear even with the administration of a low dose of vitamin D. When a preventive or therapeutic treatment of rickets by vitamin D results in a loss of appetite without any apparent cause and the appearance of apathy and a loss of weight, it is essential to discontinue vitamin D immediately. In addition, it is necessary to determine the calcium content of the blood and take a roentgenogram of the epiphyses of the tubular bones.

The treatment of hypervitaminosis D and so-called idiopathic hypercalcemia must be aimed at reducing the hypercalcemia. We apply the following measures. We immediately discontinue the administration of vitamin D and calcium preparations, as well as ultraviolet rays. Food must contain small

quantities of calcium (less than 300 milligrams daily), but at the same time the food must contain sufficient calories and animal proteins to restore the patient's weight. It is best to feed nursing babies women's milk, the calcium content of which is 25 milligrams %; in cows' milk, the calcium content amounts to 115 milligrams %, or 4.5 times more. To reduce the calcium content of cows' milk, the use of ion-exchange resins is recommended (Ye. N. Kholchol, et. al.; A. V. Ferguson; S. K. McGoven; G. Anderson, et. al.; H. G. Morgan; Th. Stapleton, et. al.). Developed in our department (Kh. Yu. Kuus) at the present time has been a procedure for obtaining cows' milk, in which the calcium content has been reduced by three to four times via the application of a KU-1 resin.

Food rich in calcium should not be eaten -- cheese, egg yolks, canned fish, caviar, beans, colored cabbage, spinach, and almonds. For the purposes of drinking and cooking, distilled water is recommended because ordinary water contains about 5-20 milligrams % of calcium. The abundant quantity of food is prescribed for the patient so as to avert the development of nephrocalcionosis.

Recommended to reduce calcium absorption is the use of cortisone (Th. Stapleton, H. G. Morgan), which, in opposition to the action of vitamin D, inhibits the absorption of calcium into the intestine. For improving the exchange of substances, it is recommended that the patient be administered an adequate amount of vitamin exchange substances (vitamins $A_1$, $B_1$, $B_2$, PP).

In prescribing vitamin D for children, a physician is obligated to prescribe the precise dose for the course of treatment and warn the parents of the harmful consequences of exceeding this dosage. For a precise dose, it is also necessary, during the writing of the prescription for vitamin D, to order a pipet.

Large doses of vitamin A inhibit the development of hypervitaminosis D (S. N. Matsko); therefore, when treating rickets, it is expedient to apply simultaneously, along with large doses of vitamin D, vitamin A in the amounts of 5,000 to 10,000 units daily (Ye. M. Lepskiy).

## CONCLUSIONS

1. The phenomena of hypervitaminosis D may develop even with insignificant overdoses of vitamin D.

2. The sensivity of infants to vitamin D can vary greatly.

3. During treatment with vitamin D, the infant should be observed closely and upon the first manifestations of hypercalcemia symptoms, vitamin D should be discontinued.

4. In prescribing vitamin D preparations for infants, it is essential to warn the parents of the dangers of overdoses.

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May 3, 1967

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ON HYPERVITAMINOSIS D AND IDIOPATHIC HYPERCALCEMIA IN YOUNG CHILDREN "

Source → Author

[Following is a translation of an article by L. A. Keres, candidate of the medical sciences, in the Russian-language periodical Sovetskaya Meditsina (Soviet Medicine), Vol 23, Moscow, June 1959, pages 35-38.] (Source)

As is known, vitamin D is accumulated in the organism, and its excessive and prolonged use may cause toxic phenomena.

The majority of pharmacology textbooks point out that a toxic dose of vitamin D exceeds by several hundred or a thousand times the therapeutic dose and that, as a consequence, hypervitaminosis D is practically never observed in children. Because of observations made in Tartu City Children's Clinic Hospital during recent years, we cannot agree with this statement. Here is an example.

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[illegible] Before her admission to the hospital, the little girl had been apathetic, at times capricious. Nor had she wanted to play or stand. Noted was the complete absence of appetite, intense constipation, exicosis (eksikoz), umusual skin dryness, and in the evenings a subfebrile temperature. The Sul'kovich urine reaction was clearly positive; in the blood serum, the quantity of inorganic calcium was 20 milligrams %. The erythrocyte sedimentation reaction ranged from 10 to 44 millimeters per hour according to Panchenko's method. Observed in the urine were traces of protein and the usual unit leukocytes; but at times a large quantity of leukocytes were encountered, as well as erythrocytes in a greatly augmented viewing field. Arterial pressure rose to 110/90 millimeters on the mercury column. Following the discontinuation of vitamin D, pathologic elements were observed in the urine for a month, the amount of clacium in the blood was raised within 1.5 months, subfebrile temperature continued for 2 months, and an accelerated erythrocyte sedimentation reaction was noted for 2.5 months.

In this manner, a mere tenfold (2 or 110X) increase in the daily therapeutic dosage of vitamin D over a four-month period caused a grave case of hypervitaminosis D in the child. X

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## CONCLUSIONS

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# CLINICAL PICTURE AND TREATMENT OF HYPERVITAMINOSIS D IN INFANTS

L. I. Bolgbarodova, A. A. Kedo

Voprosy okhrany materinstva i detstva
(Problems in Maternal and Child Welfare)
Vol. 6, 1961, pages 48-51

Russ.

The use of the usual preventive and therapeutic doses of vitamin D does not produce any side effects. At the same time experiments (S. N. Matsko, A. T. Zhmeyko, V. I. Gorbunova, Yo. S. Pevzner, G. A. Minina) and clinical tests (L. I. Gokhmeyeva, S. N. Kuritsina, V. A. Leonov, E. Yo. Mikhlin, V. A. Vlasov and V. K. Stolyarova) have established the fact that the prolonged use of large doses of vitamin D may produce hypervitaminosis with marked functional and even organic changes in the different organs and systems (liver, kidneys, cardiovascular system, metabolism, etc.). This has been confirmed by the work of a number of scientists, including L. P. Timofeyeva, V. A. Prokopchuk, Yo. S. Pevznor, G. A. Minia, Bauer and Freiberg, who have reported on the development of severe changes of an organic nature in the form of vascular sclerosis of the kidneys, heart, lungs, liver and brain in hypervitaminosis D.

With the adoption of the method of treating rickets with shock doses of vitamin D, Soviet industry has put on the open market an alcohol solution of vitamin D containing 200,000 international units per milliliter. This concentrated preparation is being used by pediatricians during recent years not only in treating but frequently in preventing rickets. It is quite natural that the use of an alcohol solution of vitamin D in the polyclinic where the control over treatment is very limited may easily lead to overdosing. This has been confirmed by our own clinical observations.

During the period 1957-1959 the clinic at our institute has had 29 infants with hypervitaminosis D under treatment. Of these 14 were between the ages of three and six months, 13 between one and nine months, one from nine to 12 months and one older than one year. Nine of the

children were on breast feeding, 10 on breast feeding with supplement, nine on artificial feeding and one on a baby diet. E464

The children were admitted to the clinic with different diagnoses: 9 -- toxic dyspepsia, 5 -- toxic pneumonia, 4 -- meningitis, 2 -- pyloric stenosis, 2 -- visceral candidamycosis, 2 for observation, one with pyuria, one with intestinal invagination, one with toxicosis of unknown etiology but only two with a correct diagnosis of hypervitaminosis D. Consequently in 27 out of 29 cases the reason for admittance was not confirmed. Twenty of the children had symptoms of severe hypervitaminosis D, eight had signs of moderately severe hypervitaminosis D and one was suffering from a mild course of the disease.

The diagnosis of hypervitaminosis D was based on careful history data, clinical and laboratory data with the decisive factors being the history and clinical picture of the disease.

Our clinical observations of patients with hypervitaminosis showed that the disease developed gradually. It was impossible from anamnestic data to determine the exact beginning of the disease. As a rule the children reached the clinic in a critical state. The principal symptom of the disease is some degree of organic intoxication with symptoms of exsiccosis. The majority of the children were somnolescent, adynamic and periodically restless. Those children in a critical condition also showed some impairment of consciousness.

An important clinical sign of hypervitaminosis D in children was impaired function of the gastrointestinal tract. There was persistent anorexia, regurgitation, vomiting and constipation. In addition to constipation the stool had a dark green color and was mucousy. Coprological examination of the feces of all children revealed a large amount of neutral fat and fatty acids. In the majority of children there was enlargement of the liver but it was reduced in size in four. This reduction in size of the liver was observed only where the course of the disease was very severe with pronounced signs of intoxication. All the sick children showed rapid weight loss, dryness of the mucosa, thirst, reduced tissue turgor -- all produced by impaired water metabolism.

The cardiovascular system showed tachycardia, systolic murmur at the apex and muted heart tones with these changes in direct proportion to the severity of the case. In the children under observation there were no marked changes in the respiratory organs.

In the clinical picture of hypervitaminosis D in children we observed a persistent renal syndrome. In all children under our observation we found polyuria and the presence of inflammatory-degenerative changes in the kidneys. The urine showed protein in amounts from trace to 1.165o/oo, there was a large amount of fatty degenerated squamous and circular epithelium, isolated hyalin and granular cylinders and almost always a large number of cylindroids. In addition there were always from

10 to 60 or even more leucocytes in the visual field and isolated fresh E465
and leached erythrocytes. The renal syndrome persisted for a long time, as a rule, even till time of discharge from the hospital. Apparently these renal lesions in hypervitaminosis D in children can be explained as degenerative changes in the renal parenchyma with diffuse calcareous infiltration and subsequent addition of inflammatory changes.

In all pediatric patients there were impairments of the vegetative nervous system which were manifest in pallor of the skin, in some children in a persistent bright red dermographism and periodic erythema-like spots. The majority of children had increased perspiration and intestinal parosis. All children showed marked muscular hypotonia and impaired motor functions, the children stopped sitting or standing, did not support themselves on their legs and could not hold up their heads.

In the great majority of children there were discernible symptoms of hypovitaminosis C, A, $B_1$ and $B_2$ manifested clinically in dryness, desquamation and itching, slight vulnerability of the visible mucosa, wrinkles at the corners of the mouth, etc.

The bones showed the following changes. In 22 children the osseous edges of the flat cranial bones were dense. The large fontanelle was comparatively small in the majority of children and was closed in two children (five and seven months old).

The children showed changes in the blood. All children revealed moderate normocytic anemia without marked changes in the white blood cells. Accelerated sedimentation rate for erythrocytes was persistent and stable. Some children were discharged with an accelerated erythrocyte sedimentation rate without any other symptoms of hypervitaminosis D. In the majority of children the amount of calcium in the blood increased to 11-17 mg%.

The phosphorus content of the blood dropped in the children.

In 22 children blood sugar was determined on an empty stomach with 10 showing an increase (from 107 to 232 mg%) and 12 showing average readings. The degree of increase in blood sugar in children with hypervitaminosis D depended directly on the severity of the disease. We may assume that the increase in blood sugar in severely involved children was caused not only by impaired pancreatic function but by impairment of the assimilatory function of the liver. The sugar lines are to some degree confirmed by this assumption. As the general condition of the children improved the blood sugar level approached the normal.

A blood cholesterol analysis of 27 children showed 21 children with a higher cholesterol level (from 165 to 300 mg%). Some regularity for this change was observed, namely that the more severe the clinical course of the hypervitaminosis D the higher the blood cholesterol level. It should be pointed out that clinical symptoms of hypervitaminosis D

leveled out and disappeared before the cholesterol content of the blood reached normal. In some children discharged between the 42nd and 50th day the cholesterol level still remained high (more than 200 mg%). The increase in blood cholesterol in children with hypervitaminosis D indicates impaired hepatic function.

The severity of the course of this disease depends, as a rule, directly on the amount of vitamin D taken by the child. The disease was the most severe in children who had taken an alcohol solution of vitamin D in a ratio of 1,100,000 to 1,800,000 international units per kilogram of body weight.

According to the data furnished by a number of Soviet scientists (M. S. Maslov, A. F. Tur, Ye. M. Lepskiy, E. M. Kravets) there will be no symptoms of hypervitaminosis D when giving doses of 25,000 international units of vitamin D for 40-45 days if we prescribe no more than 250,000 international units per kilogram of body weight for the course of treatment.

In treating hypervitaminosis D, depending on the severity of the patient's condition and the individual features of the course of the disease, we used combined therapy aimed during the first stage of the disease at eradicating toxicosis and dehydration of the body. For this purpose the children were provided with optimal environmental conditions, individual care and satisfactory aeration. All the patients were given enough liquid (tea or 5% glucose) for a day's requirements per os with a single intravenous infusion or, in severe cases, intravenous drip administration of enough fluid for one, two or three days. The main nourishment was mother's milk. From the very first days in the ward the children were given intravenously plasma and a 5% glucose solution with 200 mg vitamin C and 10-15 mg vitamin $B_1$ per 24 hours. Insulin-glucose therapy was widely used during the first stage of treatment.

For a long time the sick children were given 2-3 drops (600-900 international units) of vitamin A and 10-20 mg of vitamin PP per day.

During the second stage of therapy, i.e., after intoxication was neutralized, all measures were aimed at increasing the body's immunological power, further restoring the functions of the different body organs and systems and increasing metabolism. The sick children were given vitamins $B_6$ and $B_{12}$, blood transfusions, enzymes, etc. Massage and exercise were widely used.

The diet of the pediatric patients was gradually extended and by the end they had reached a diet appropriate for their ages.

The therapy which we practiced gave positive results. All the children under our observation recovered. Later catamnestic observations completely justified the effectiveness of our therapy.

## CONCLUSIONS

1. The use of vitamin D for therapy in larger than established therm[illegible]ic doses may cause hypervitaminosis D in children.

2. Hypervitaminosis D in children is characterized clinically by intox[illegible]ion, impaired nervous function, disorders of the gastrointestinal t[illegible] endocrine system, blood system, cardiovascular, urinary and skelet[illegible] systems and changes in the water, mineral, carbohydrate and lipid [illegible]etabolism.

3. We found a direct relationship between the severity of the disea[illegible] the degree of impairment of functions and metabolism and the amount [illegible]f vitamin D taken. The higher the dose of vitamin D per kilogram of bo[illegible]weight, the more severe the course of the disease.

4. Treatment for hypervitaminosis D in children should be over-all and b[illegible]stages. When the sick child is admitted all attention should be direct[illegible] toward eliminating the toxicosis and dehydration and toward restor[illegible]organ and system functions and metabolism as a whole.

5. The effectiveness of therapy for children with hypervitaminosis D dep[illegible]s largely on prompt recognition of the disease.

6. The use of an alcohol solution of vitamin $D_2$ for treating rickets in children must be under the strict control of a pediatrician.

7. Free sale of an alcohol solution of vitamin $D_2$ in drug stores must be prohibited.

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# ИНИЧЕСКАЯ КАРТИНА И ЛЕЧЕНИЕ ГИПЕРВИТАМИНОЗА D У ДЕТЕЙ РАННЕГО ВОЗРАСТА

*Л. И. Белобородова, А. А. Кедо*

1-й кафедры детских болезней (зав.—проф. П. А. Шалков) Ленинградского ордена нина института усовершенствования врачей имени С. М. Кирова (дир.—доцент Е. Кнеселе) и объединенной детской больницы имени К. А. Раухфуса (главный врач Ю. С. Чистякова)

Применение обычно принятых профилактических и лечебных доз тамина D не вызывает каких-либо побочных явлений. В то же время кспериментально (С. Н. Мацко, А. Т. Жмейдо, В. И. Горбунова, С. Певзнер, Г. А. Минина) и клинически (Л. И. Гокинаева, С. Н. Кучина, В. А. Леонов, Э. Е. Михлин, В. А. Власов и В. К. Столпрова) становлено, что длительное применение больших доз витамина D может привести к развитию гипервитаминоза D с глубокими функциональными и даже органическими изменениями со стороны различных органов и систем (печени, почек, сердечно-сосудистой системы, обмена щества и т. д.). Это подтверждается работами ряда авторов, в том числе Л. П. Тимофеевой, В. А. Прокопчук, Е. С. Певзнер, Г. А. Мининой, Фауэр и Фрейберг, которые сообщили о развитии весьма тяжелых изменений органического характера в виде склероза сосудов почек, сердца, егких, печени и мозга при гипервитаминозе D.

С внедрением в [illegible] рахита ударными дозами
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ажу спиртовой ра[illegible]
Этот концентриров[illegible]
в последние годы и[illegible]
аже и для профил[illegible]
спиртового раствор[illegible]
оль за проведени[illegible]
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ными наблюдения[illegible]

С 1957—1959
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Диагноз ги
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болезни.

Наши клин
показали, что з
его начало ана
купали, как пр
вания являлас

ганизма с явлениями экзикоза. У большинства детей отмечалась сон
мость, адинамия, периодическое беспокойство. У детей, находящих
в тяжелом состоянии, наблюдалось в той или иной степени наруше
сознания.

Важным клиническим признаком при гипервитаминозе D у де
было нарушение функции желудочно-кишечного тракта. Отмечал
наличие упорной анорексии, срыгиваний, рвоты и запора. Наряду с
явлением запора стул у больных приобретал темно-зеленую окраск
был слизистый. При копрологическом исследовании кала у всех де
были в значительном количестве обнаружены нейтральный жир и ж
гие кислоты. У большинства детей печень была увеличена, а у 4—умо
шена. Уменьшение печени наблюдалось только при очень тяжелом
чении заболевания с резко выраженными признаками интоксикаци
У всех больных детей наблюдалась быстрая потеря веса, сухость сли
тых, жажда, пониженный тургор тканей, что обусловлено нарушени
водного обмена.

Со стороны сердечно-сосудистой системы отмечались тахикар
систолический шум на верхушке и приглушение тонов сердца, при
эти изменения находились в прямой зависимости от тяжести слу
Каких-либо отчетливых изменений со стороны органов дыхания у
блюдаемых нами детей отметить не удалось.

В клинической картине гипервитаминоза D у детей мы наблюд
постоянный почечный синдром. У всех детей, бывших под наблюдени
отмечались полиурия и наличие воспалительно-дегенеративных изм
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# КЛИНИЧЕСКАЯ КАРТИНА И ЛЕЧЕНИЕ ГИПЕРВИТАМИНОЗА D У ДЕТЕЙ РАННЕГО ВОЗРАСТА

*Л. И. Белобородова, А. А. Кедо*

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С внедрением в практику метода лечения рахита ударными дозами витамина D отечественная промышленность выпустила в свободную продажу спиртовой раствор витамина D, содержащий 200 000 ИЕ в 1 мл. Этот концентрированный препарат применяется врачами-педиатрами за последние годы не только с лечебной целью, но нередко используется даже и для профилактики рахита. Вполне естественно, что применение спиртового раствора витамина D в поликлинических условиях, где контроль за проведением лечения весьма ограничен, может легко привести к передозировке препарата. Это подтверждается и нашими клиническими наблюдениями.

С 1957—1959 гг. в клинике института находилось на излечении 29 детей раннего возраста с гипервитаминозом D. Из них в возрасте от 3 до 6 месяцев было 14 детей, от 1 до 9 месяцев — 13, от 9 до 12 месяцев — один ребенок и старше года — один ребенок. На грудном вскармливании находилось 9 детей, на грудном вскармливании с прикормом — 10, на искусственном вскармливании — 9 детей и один ребенок находился на малоточном столе.

В клинику больные дети поступали с различными диагнозами: токсическая дистрофия — 9, токсическая пневмония — 5, менингит — 1, пилоростеноз 2, висцеральный кандидамикоз — 2, для обследования — 2, пиурия — один, кишечная инвагинация — один, токсикоз неясной этиологии — один ребенок и только у 2 больных был поставлен правильный диагноз гипервитаминоза D. Следовательно, в 27 случаях из 29 диагноз направления в клинике не подтвердился. С тяжелыми проявлениями гипервитаминоза D было 20 детей, с заболеваниями средней тяжести — 8 детей и сравнительно с легким течением — один ребенок.

Диагноз гипервитаминоза D ставился на основании тщательно собранного анамнеза, клинических и лабораторных данных, причем решающим в постановке диагноза являлись анамнез и клиническая картина болезни.

Наши клинические наблюдения за больными гипервитаминозом показали, что заболевание это развивалось исподволь. Точно установить его начало анамнестически не удавалось. В клинику же больные дети поступали, как правило, в тяжелом состоянии. Ведущим признаком заболевания являлась в той или иной степени выраженная интоксикация ор-

ганизма с явлениями экземоза. У большинства детей отмечалась сонливость, адинамия, периодическое беспокойство. У детей, находящихся в тяжелом состоянии, наблюдалось в той или иной степени нарушение сознания.

Важным клиническим признаком при гипервитаминозе D у детей было нарушение функции желудочно-кишечного тракта. Отмечалось наличие упорной анорексии, срыгиваний, рвоты и запора. Наряду с появлением запора стул у больных приобретал темно-зеленую окраску и был слизистый. При копрологическом исследовании кала у всех детей были в значительном количестве обнаружены нейтральный жир и жирные кислоты. У большинства детей печень была увеличена, а у 4—уменьшена. Уменьшение печени наблюдалось только при очень тяжелом течении заболевания с резко выраженными признаками интоксикации. У всех больных детей наблюдалась быстрая потеря веса, сухость слизистых, жажда, пониженный тургор тканей, что обусловлено нарушением водного обмена.

Со стороны сердечно-сосудистой системы отмечались тахикардия, систолический шум на верхушке и приглушение тонов сердца, причем эти изменения находились в прямой зависимости от тяжести случая. Каких-либо отчетливых изменений со стороны органов дыхания у наблюдаемых нами детей отметить не удалось.

В клинической картине гипервитаминоза D у детей мы наблюдали постоянный почечный синдром. У всех детей, бывших под наблюдением, отмечались полиурия и наличие воспалительно-дегенеративных изменений в почках. В моче определялся белок от следов до 1,165‰, имелся в большом количестве жирно перерожденный плоский и круглый эпителий, единичные гиалиновые и зернистые цилиндры и почти всегда большое количество цилиндроидов. Кроме того, постоянно обнаруживались лейкоциты от 10 до 80 и больше в поле зрения, единичные свежие и выщелоченные эритроциты. Почечный синдром держался, как правило, длительно, вплоть до выписки из больницы. По-видимому, указанные почечные изменения при гипервитаминозе D у детей объясняются дегенеративными изменениями почечной паренхимы с рассеянной известковой инфильтрацией и последующим присоединением к ним воспалительных изменений.

У всех больных детей имелись нарушения со стороны вегетативной нервной системы, которые проявлялись в бледности кожных покровов, у некоторых детей — в ярком стойком красном дермографизме и периодически появляющихся эритемоподобных пятен. У большинства детей отмечались повышенная потливость и парез кишечника. У всех детей отчетливо наблюдались выраженная мышечная гипотония и нарушение двигательных функций, дети переставали сидеть, стоять, не опирались на ножки и не удерживали головку.

У значительного большинства детей обнаруживались симптомы гиповитаминоза С, А, В и $B_2$, клинически проявляющиеся в сухости, шелушении и зуде кожных покровов, легкой ранимости видимых слизистых оболочек, появлении трещин у углов рта и т. д.

Со стороны костной системы отмечены следующие изменения. У 22 детей костные края плоских костей черепа были плотными. Большой родничок у большинства детей был сравнительно малых размеров, а у 2 детей (5 и 7 месяцев) был закрыт.

У больных детей наблюдались изменения со стороны крови. У всех детей была обнаружена умеренная нормохромная анемия без отчетливых сдвигов со стороны белой крови. Ускоренная РОЭ — от 10 до 60 мм в час — держалась стойко и длительно. Несколько детей было выписано из больницы с ускоренной РОЭ при отсутствии у них каких-либо других симптомов гипервитаминоза D. У большинства больных детей было увеличено количество кальция в крови до 11—17 мг%.

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Содержание фосфора в крови у детей было понижено.

У 22 детей определялся натощак сахар крови, при этом оказалось, что у 10 из них сахар крови был повышен (от 107 до 232 мг%), а у остальных 12 детей он находился в пределах нормы. Степень повышения сахара крови у детей с гипервитаминозом D находилась в прямой зависимости от тяжести заболевания. Надо полагать, что отмеченное повышение сахара крови у тяжелобольных детей с гипервитаминозом D обусловлено не только нарушением функции поджелудочной железы, но также и нарушением ассимиляторной функции печени. Полученные сахарные кривые в какой-то степени подтверждают данное предположение. С улучшением общего состояния детей сахар крови приходил к норме.

У 27 детей определялся холестерин в крови, при этом оказалось, что у 21 больного он был повышен (от 166 до 300 мг%). Определялась некоторая закономерность в изменении этого показателя у больных, а именно, чем тяжелее было клиническое течение гипервитаминоза D, тем выше был холестерин крови. Следует отметить, что клинические симптомы гипервитаминоза D сглаживались, исчезали раньше, чем нормализовалось содержание холестерина в крови. У части детей, которые были выписаны на 42—50-й день заболевания, холестерин крови оставался еще повышенным (более 200 мг%). Повышенное содержание холестерина в крови у детей с гипервитаминозом D указывает на нарушение функции печени.

Тяжесть течения данного заболевания находится, как правило, в прямой зависимости от количества принятого ребенком витамина D. Наиболее тяжело протекало заболевание у детей, которые получили спиртового раствора витамина D от 1 100 000 до 1 800 000 ИЕ на 1 кг веса тела.

Согласно данным ряда отечественных авторов (М. С. Маслов, А. Ф. Тур, Е. М. Ленский, Э. М. Кравец), при дозировке витамина D у детей на курс лечения 40—45 дней по 25 000 ИЕ, если назначать его не больше 250 000 ИЕ на 1 кг веса на курс, явлений гипервитаминоза D не наступает.

При лечении детей, больных гипервитаминозом D, в зависимости от тяжести состояния, индивидуальных особенностей течения болезни во всех случаях применялась комплексная терапия, направленная в первом этапе болезни на устранение токсикоза и дегидратации организма. С этой целью больным детям создавались оптимальные условия внешней среды, обеспечивался индивидуальный уход и достаточная аэрация. Все больные обеспечивались достаточным количеством жидкости (чай или 5% глюкоза) до суточной потребности через рот, одномоментным внутривенным вливанием или в тяжелых случаях с помощью аппарата внутривенного капельного вливания на 1, 2, 3 суток. Основным питанием являлось грудное молоко. С первых же дней пребывания больных детей в отделении они получали внутривенно плазму и 5% раствор глюкозы с витаминами С—200 мг, $B_1$—10—15 мг в сутки. Широко применялась на первом этапе лечения инсулино-глюкозная терапия.

Больные дети получали длительное время витамин А по 2—3 капли (600—900 ИЕ) и витамин РР—10—20 мг в сутки.

На втором этапе лечения, т. е. после снятия интоксикации, все мероприятия были направлены на поднятие иммунобиологических сил организма, дальнейшее восстановление функции различных органов и систем и обмена веществ. Больные дети получали витамины $B_6$, $B_{12}$, трансфузии крови, ферменты и т. д. Широко применялись массаж и гимнастика.

Постепенно расширялась диета больных детей и в конце концов они переводились на питание, соответствующее возрасту.

Проводимая нами терапия дала положительные результаты. Все находившиеся под нашим наблюдением дети выздоровели. Последующие катамнестические наблюдения вполне подтверждали эффективность проведенной терапии.

## Выводы

1. Применение с лечебной целью витамина D выше установленных лечебных доз может вызывать у детей гипервитаминоз D.

2. Гипервитаминоз D у детей клинически характеризуется интоксикацией организма, нарушением функции нервной системы, желудочно-кишечного тракта, эндокринной системы, системы крови, сердечно-сосудистой мочевыделительной и костной систем, а также изменением водного, минерального, углеводного и липоидного обмена вещества.

3. Выявлена прямая зависимость между тяжестью заболевания, степенью нарушений функции органов и обмена вещества и количеством принятого витамина D. Чем больше была превышена доза витамина D на 1 кг веса тела, тем тяжелее протекало заболевание.

4. Лечение гипервитаминоза D у детей должно быть комплексным и этапным. При поступлении больного ребенка все внимание должно быть обращено на снятие токсикоза и обезвоженности организма и восстановление функций органов, систем и обмена веществ в целом.

5. Эффективность проводимой терапии при гипервитаминозе D у детей в значительной степени зависит от своевременного распознавания болезни.

6. Употребление спиртового раствора витамина $D_2$ для лечения рахита у детей должно проводиться под строгим контролем врача-педиатра.

7. Свободная продажа спиртового раствора витамина $D_2$ в аптеках должна быть запрещена.

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## CLINICAL PICTURE AND TREATMENT OF D-HYPERVITAMINOSIS IN INFANTS

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### Summary

With the appearance for sale of concentrated vitamin D solutions D-hypervitaminosis cases among infants began to increase in their frequency. Within the past 3 years 29 children were observed at the clinic, all of them suffered from this affection, assuming various degrees of severity. On the basis of clinical observations the authors present a detailed clinical picture of lesions in the lungs accompanying moderate and severe hypervitaminosis in infants. A distinct direct relationship was noted between the severity of the disease and the amount of vitamin D received by the child per kg of body weight.

Measures of treatment and prevention of mild and severe forms of D hypervitaminosis are recommended.

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# The Pathogenesis of Idiopathic Hypercalcemia in Infancy

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With the Technical Assistance of I. W. J. Evans

THE PURPOSE of this article is to review the chemical changes which have been found in cases of idiopathic hypercalcemia, and to discuss the etiology and treatment of the disease. The clinical features have been described elsewhere.[1] In summary, all cases have commenced in the first year of life, sometimes as early as a few weeks after birth, but usually at about five months, with anorexia, vomiting, constipation and failure to gain weight normally. Some cases have one or more of the following features: thirst, polyuria, occasional spikes of fever, a systolic murmur, hypertension, osteosclerosis, a peculiar facies and mental retardation.[2] In general it can be said that the earlier the onset and the more severe the symptoms, the more likely are complicating features to be present.

## CHEMICAL DESCRIPTION

The characteristic chemical changes are a rise in the level of serum calcium and blood urea. Other changes may occur as well: hypercholesterolemia, rise in $\alpha_2$ globulin, acidosis, and a low serum alkaline phosphatase.

### *Calcium*

Because of the possibility of an inaccurate laboratory estimation and because a transient rise in the serum calcium level can occur in other diseases, we have only considered the diagnosis of idiopathic hypercalcemia when two estimations of the serum calcium have been at least 12 mg/100 ml. The highest recorded value is 23 mg/100 ml by Cordeiro,[3] but in the United Kingdom the highest is 19 mg/100 ml.[4] The distribution of the increase of serum calcium between the protein-bound and soluble fractions has not been determined. There is no constant relationship between the degree of hypercalcemia and plasma protein levels. The daily excretion of calcium in the urine is raised. Amounts as large as 148 mg in 24 hours have been found.[5] Other reports[4,6,7,8] all give figures well above the normal daily excretion which is of the order of 20 to 30 mg.[5]

In spite of the increased urinary calcium excretion, the calcium balance is strongly positive (Fig. 1). In reported balance studies the calcium retention expressed as a percentage of calcium intake has varied between 31 and 69 per cent in eleven cases, with an average of 49 per cent.[4,5,6,8]

### *Phosphorus*

The serum phosphorus is usually in the normal range of 3.5 to 5.5 mg/100 ml sometimes slightly higher, sometimes lower. In the early stages of the illness, when the impairment of renal function is minimal, there appears to be no constant relationship to the serum calcium level. In the more advanced stage of the illness the serum phosphorus may be abnormally high.

When the serum calcium is high, the phosphorus balance is strongly positive (Fig. 1). In seven reported balance studies,[4,5,8] the phosphorus retention expressed as a percentage

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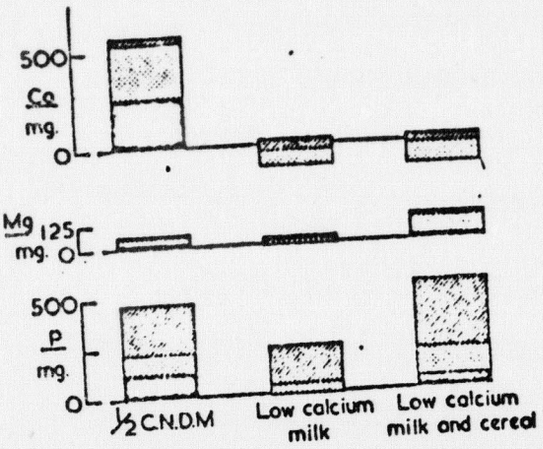


Fig. 1. Treatment related to daily calcium, magnesium and phosphorus balances, which are averages of four-day collections. (Urinary excretion hatched, stool excreted dotted, positive balance black). (From: *Lancet* 1: 932, 1956.)

of phosphorus intake has varied between 26 and 84 per cent with an average of 51 per cent.

### *Magnesium*

We have estimated the serum magnesium in seven children. Values ranged from 1.8 to 2.7 mg/100 ml, confirming the findings of other workers.[8] In only one case did there appear to be any relation with the rise and fall of serum calcium (Fig. 2) and in that patient the magnesium also paralleled the changes in serum phosphate and urea. It therefore seems likely that the changes were due to fluctuations in renal function. The magnesium balance seems to be unaffected throughout the course of the illness[8,9] (Fig. 2).

### *Bicarbonate*

In most cases of idiopathic hypercalcemia the serum bicarbonate is within normal limits. Some infants may have an abnormally low serum bicarbonate even when renal function is not greatly impaired.[10] It is possible that some infants with hypercalcemia have an associated renal acidosis.[11] There appears to be no direct relationship between serum calcium and bicarbonate.

### *Sodium, Potassium Chloride*

The serum concentration of these electrolytes are within normal limits in idiopathic hypercalcemia of infancy. There is no disturbance of the sodium, chloride or potassium balances.[9]

### *Proteins*

In his original description of the biochemical changes in idiopathic hypercalcemia, Payne[11] stated that the plasma proteins showed an in-

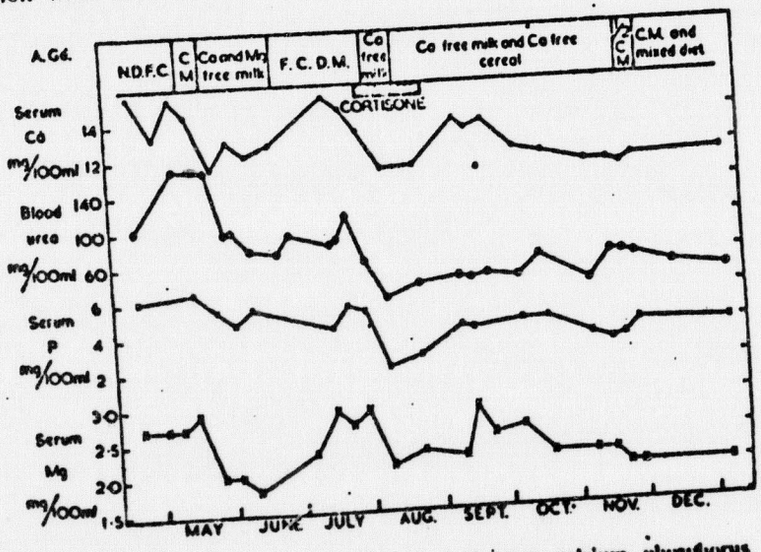


Fig. 2. Treatment related to blood urea, and serum calcium, phosphorus and magnesium. (Modified from *Acta Paediat.* 44: 559, 1955.)

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crease in the $\alpha_2$- and $\gamma$-globulin fractions. These findings have been confirmed by other investigators, but only in some cases of idiopathic hypercalcemia.[6,12] Only two out of seven infants studied by us have had total serum proteins higher than 7 g/100 ml, but in all of the seven the $\alpha_2$-globulin fraction was significantly raised, although the $\gamma$-globulin was normal. The $\alpha_1$- and $\beta$-fractions are occasionally slightly raised.

*Cholesterol*

In severe cases serum cholesterol levels may be of the order of 300 to 400 mg/100 ml. In infants with an illness of intermediate severity, the serum cholesterol is often increased to 250 to 300 mg/100 ml, and returns to normal levels when the serum calcium falls and clinical improvement commences.

TABLE I

Serum Calcium Levels Related to Serum Citrate Levels and Diet

| Patient | Diet | Serum calcium mg/100 ml | Serum citrate mg/100 ml |
|---|---|---|---|
| C. Hm. | Vitamin D fortified dried milk | 13.4 | 3.0 |
| | Low-calcium diet | 12.0 | 1.5 |
| | Low-calcium diet with added solids | 12.1 | 3.0 |
| | Low-calcium diet with added solids | 11.2 | 1.8 |
| S. Fk. | Vitamin D fortified dried milk | 13.1 | 2.7 |
| | Low-calcium diet | 11.1 | 2.2 |
| J. Ch. | Vitamin D fortified dried milk | 13.2 | 2.6 |
| | Vitamin D fortified dried milk | 12.1 | 2.0 |
| | Low-calcium milk | 11.1 | 1.9 |
| | Low-calcium milk | 11.0 | 1.3 |
| | Equal parts whole milk and low-calcium milk | 11.7 | 2.7 |
| A. Pr. | Vitamin D fortified dried milk | 15.1 | 3.1 |
| | Vitamin D fortified dried milk | 13.7 | 2.8 |
| | Low-calcium diet | 11.8 | 3.5 |
| | Low-calcium diet | 12.7 | 2.1 |
| | Low-calcium diet | 12.2 | 2.0 |
| | Low-calcium diet | 11.5 | 1.7 |
| | Low-calcium diet with added solids | 11.2 | 4.0 |
| | Low-calcium diet with added solids | 10.9 | 3.6 |

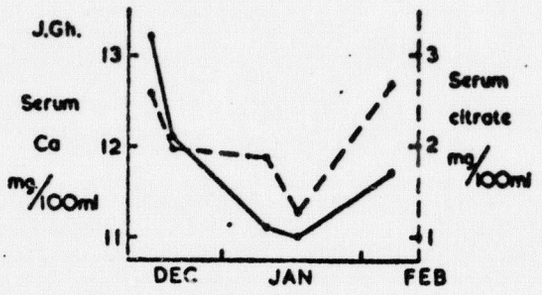


Fig. 3. The variable relationship between the serum citrate and serum calcium levels.

*Alkaline Phosphatase*

Low concentrations of this enzyme are often found in the active phase of the disorder, particularly in severely affected cases when osteosclerosis is a complicating feature. Levels of 4 to 8 King-Armstrong units are not uncommon. The concentrations return to normal during recovery and sometimes become higher than normal when affected children are treated with calcium-free diets, and radiologic evidence of a decrease in osteosclerosis develops.

*Citrates*

It has been stated that the serum citrate level is inversely related to the serum calcium.[8] In four cases studied by us no constant relationship has been found. (Table I and Fig. 3,4).

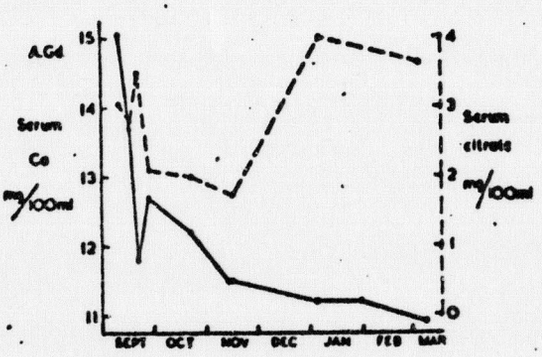


Fig. 4. The variable relationship between the serum citrate and serum calcium levels.

*Urea*

The blood urea is raised, although not necessarily throughout the whole active course of the disease. In some infants it is of the order of 160 to 180 mg/100 ml even in the absence of dehydration.

*Vitamin A*

Plasma vitamin A levels were estimated in eight infants with idiopathic hypercalcemia and were significantly higher than those found in normal infants, or in marasmic infants, both in the fasting state and four hours after a standard oral test dose of vitamin A.[14]

## PATHOGENESIS

The clinical, chemical and pathologic findings closely resemble those which are found in persons who have received excessive intakes of vitamin D. (Fig. 5) The following evidence suggests that a large intake of vitamin D is a main causative factor:

(1) All infants with the disease have received vitamin D either as a supplement or in a fortified infant food.

(2) The vitamin D intake of infants in the United Kingdom, where the disease has been commonest, has increased during the past fifteen years largely as a result of the increased fortification of infant foods; the extent of this increase was not fully appreciated until recently. This is shown in the tables reproduced from the report by a sub-committee of the British Paediatric Association[15] (Tables II, III). These figures permit an approximate estimate to be made of the likely intake of vitamin D of an infant fed on the full-cream milk, referred to in Table II fortified with crystalline calciferol 460 I.U. per dry ounce, the calciferol-fortified cereal referred to in Table III, together with the generally recommended quantity of cod-liver oil compound:

For example, the vitamin D intake of an infant who receives each day

| | *Approximately* |
|---|---|
| (a) 1⅓ pints of a full-cream dried milk containing 460 I.U. vitamin D per dry oz | 1,725 I.U. |
| (b) 1 oz of a cereal containing 1,500 I.U. vitamin D per dry oz | 1,500 I.U. |
| (c) 1 teaspoonful of national cod-liver oil compound (Welfare Food Service) would be about 4,000 I.U. | 700 to 800 I.U. |

(3) The disorder has occurred in Finland, especially among premature babies who have had interstitial plasma cell pneumonia. These infants had all received several hundred thousand units of vitamin D as stoss therapy.[16,17]

An excessive vitamin D intake, however, cannot be the sole factor leading to the development of the disorder, because thousands of infants in the United Kingdom and elsewhere must have received as large doses of vitamin D as those few hundreds who have developed the disease; and some infants with the disease have not received excessive doses of vitamin D. Some infants have been affected in the early weeks of life. These three facts suggest that idiopathic hypercalcemia may be due to the par-

TABLE II

The Amounts of Crystalline Calciferol Added to a Proprietary Brand of Full-Cream Dried Milk, and Reports of Assays of Vitamin D in the Milk

| Date | Crystalline Calciferol added *I.U./dry oz* |
|---|---|
| Up to August 1942 | 70 |
| From August 1942 | 128 |
| From October 1943 | 403 |
| From November 1944 | 460 |
| From October 1954 | 690 |

| Age of milk months | Year of manufacture | Assays |
|---|---|---|
| 7 to 12 | 1950 | 362 |
| 13 to 18 | 1952 | 463 |
| | | 405 |
| 3 to 6 | 1952 | 560 |

TABLE III

The Amount of Calciferol Added to a Dried Cereal and Reports of Assays

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| Date | Crystalline Calciferol added *I.U./dry oz* | Assays | |
|---|---|---|---|
| | | Age of feed months | *I.U./dry oz* |
| Up to March 1946 | 1,000 | | |
| From March 1946 | 2,000 | 0 to 2 | 1,110 to 1,870 |
| | | 13 to 28 | 758 to 1,210 |

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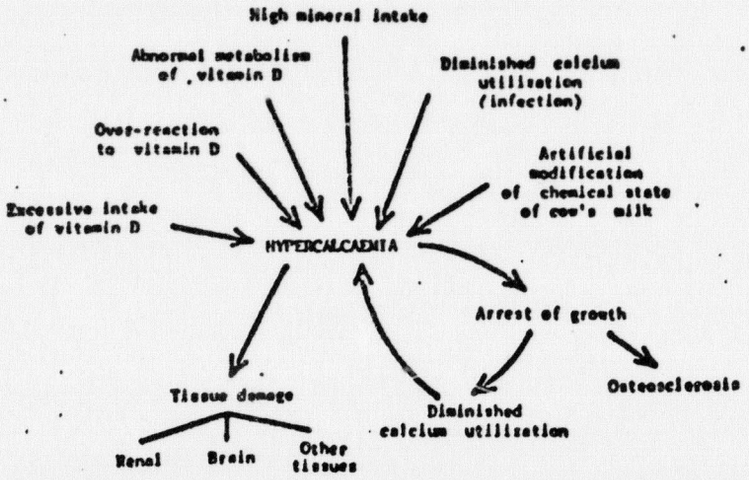


Fig. 5. The pathogenesis of idiopathic infantile hypercalcemia (Modified[18] from Helvet. Paediat. Acta 10: 149, 1955.)

ticular response of some infants to vitamin D, either an extreme of the physiologic variation, or an inborn metabolic defect which causes them to react in an abnormal manner.[14,19]

The fall in the high serum calcium when cortisone is given resembles that observed in sarcoidosis with hypercalcemia.[20] In both instances, it may be caused by an anti-vitamin D effect.

*Conditioning Factors*

Alternatively, or in addition, there may be conditioning factors which make some infants more susceptible to a given dose of vitamin D.

(1) All the infants reported as suffering from idiopathic hypercalcemia have been artificially fed. The high calcium and phosphorus content of cow's milk (approximately 120 mg/100 ml and 95 mg/100 ml, respectively), compared to those in human milk (approximately 30 mg/100 ml and 15 mg/100 ml, respectively) must at least predispose to the development of the disease.

(2) Impaired rates of growth lower the net requirement of calcium, phosphorus and vitamin D. This was probably a factor in the infants who had had interstitial plasma cell pneumonia reported from Finland.[16] Infections have preceded the onset of the disease in cases reported from the United Kingdom.[6,21]

(3) Idiopathic hypercalcemia has been recognized in infants in many countries (Finland, Norway, Portugal, Sweden, Switzerland, United Kingdom and United States of America). Although the vitamin D fortification of milk is much less in America than it has been in the United Kingdom, many American mothers must have given their infants supplementary vitamin preparations; the disease has not been overlooked, yet the number of cases apparently has been small. A possible explanation may be in the use of evaporated milks in the North American Continent, whereas in the United Kingdom dried milks are in general use. It has been suggested that the essential fatty acid content of dried milks may be lower than that of evaporated milks,[22] (both, of course, being cow's milk, have a lower essential fatty acid content than human milk). This is an attractive hypothesis which would explain the geographic distribution of the illness, and might help to account for the high plasma cholesterol levels found in affected infants, as there is some evidence that a deficiency of essential fatty acids interferes with sterol metabolism and can be followed by a raised plasma cholesterol.[23–25] Sinclair's claim is not supported by analyses of different preparations of cow's milk for their essentially fatty acid contents.[26]

While investigating this problem we have made an interesting observation. An infant with idiopathic hypercalcemia and an infant

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Fig. 6. Section of kidney stained for calcium from a female infant with idiopathic hypercalcemia who died at age of 11 months (no treatment having been given for comparison with Figure 7).

Fig. 7. Section of kidney from a rat six weeks old which had been given 500,000 units calciferol 12 days previously. (Alizarin × 10.)

with a normal serum calcium level were given by mouth cotton seed oil, which is rich in essential fatty acids. In both instances there was a fall in the serum calcium level, with a rebound on discontinuing the oil.

The raised vitamin A levels in idiopathic hypercalcemia[14] support the possibility of abnormal fat metabolism in this disease.

## COMPLICATIONS

The complications of idiopathic hypercalcemia appear to be due to the high serum calcium, its duration of action, and the age of the infant when it develops. The type of complication is determined by the location of metastatic calcification in the body and the overall effect of calcium on tissue metabolism.

### *Kidneys*

Renal involvement is evidenced by azotemia. Calcification and fibrosis of the kidneys have been reported by several investigators,[2,7,13,17-20] and it seems that this organ is the most constant site of calcium deposition. Calcium deposits are concentrated at the cortico-medullary junctions (Figures 6, 7), and are seen as concretions within the lumina of the tubules and as amorphous deposits in the interstitial tissue. Similar changes at this site occur in rats given toxic doses of vitamin D, and also in rats given smaller doses of vitamin D together with acetazolamide.[21]

### *Renal Function*

The high blood urea may fall to normal limits after two to three weeks of treatment independently of hydration changes. This is in keeping with the improvement in renal function (Table IV), and resembles that which occurs in sarcoidosis with hypercalcemia following treatment.[22] It seems unlikely that kidneys with the severe damage and fibrosis seen in some

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fatal cases of idiopathic hypercalcemia could improve to this extent in such a short time, and it is probable that earlier and reversible changes occur. There might be a clearing of kidney tubules obstructed by calcium casts as has been reported in vitamin D poisoning studied by renal biopsy.[22] The impaired inulin and urea clearances which improve during treatment would support this theory, unless altered permeability of tubular epithelium in this disease nullifies the clearance results. An alternative or additional explanation is that a high level of ionized calcium may inhibit enzyme activity in renal tubular cells without causing irreversible changes.

Our experiments done on young rats poisoned with vitamin D and receiving a high-calcium diet show no reduction in the oxygen uptake of kidney slices. The oxygen uptake of kidney slices of healthy young rats is not diminished by the addition of high concentrations of calcium or vitamin D to the Krebs-Ringer medium. These experiments, however, do not deny the possibility of a lesser degree of inhibition of metabolic processes not directly concerned with aerobic oxidation, but with more specialized organ function.

Vitamin D in its soluble phosphorylated form is an activator of aerobic oxidation in tissues other than bone, as well as being an activator of other enzymes such as alkaline phosphatase.[24] Thus it is reasonable to assume that if a depression of tissue metabolism occurs in hypercalcemia it is more likely to be due to the hypercalcemia than to a primary vitamin D effect.

### *Other Sites of Calcification*

Calcification of blood vessels[27] of the myocardium and heart valves[12,29] and in subcutaneous tissues[25] have been described. Osteosclerosis is a common feature in the more severe grades of the illness. Calcification has also been found in the lungs and the fundal glands of the stomach.[13]

The systolic murmur which is frequently found in affected infants may be due to calcification in cardiac valves, the hypertension to thickening or calcification of arterial walls.

TABLE IV

Renal Function Tes[illegible]

C. Hm. (Female)

| Age in Months | Serum calcium mg/100 ml | Blood urea mg/100 ml | Urine specific gravity | Inulin clearance | | | | | | Urea clearance | | | | | | Urea clearance-inulin clearance ratio |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | U mg/100 | V ml | P mg/100 ml | Time mins | Uncorrected ml/min | Corrected To surface area 1.73 M² ml/min | U mg/100 | V ml | P mg/100 ml | Time mins | Uncorrected ml/min | Corrected To surface area 1.73 M² ml/min | |
| 10 | 13.4 | 70 | 1.014 (19 hr) | 391 | 57.5 | 58 | 60 | 6.5 | 34 | 465 | 57.5 | 71 | 60 | 6.3 | 33 | 1.03 |
| | | | | 540 | 49 | 63 | 60 | 7.1 | 37 | 563 | 49.0 | 69 | 60 | 6.7 | 35 | 1.05 |
| 10½ | 12.0 | 68 | 1.010 (14 hr) | 300 | 63 | 33 | 82 | 7.0 | 37 | 565 | 63 | 68 | 82 | 6.4 | 33 | 0.90 |
| 13 | 11.2 | 58 | 1.022 (18 hr) | 398 | 62 | 29 | 70 | 12.1 | 56 | 550 | 62 | 53 | 70 | 8.4 | 39 | 0.69 |
| | | | | 413 | 64 | 30 | 90 | 14.9 | 70 | 470 | 64 | 53 | 60 | 8.6 | 40 | 0.53 |
| 20 | 10.8 | 42 | 1.022 (15 hr) | 222 | 112 | 18 | 60 | 23.0 | 83 | 410 | 112 | 46 | 60 | 16.6 | 60 | 0.72 |
| | | | | 616 | 54 | 16 | 70 | 30.1 | 108 | 860 | 54 | 46 | 70 | 14.4 | 52 | 0.47 |

* The clearances were done when the infant was sedated with a barbiturate. The urine volumes include the 30 ml. water used for bladder washings. Note the low inulin and urea clearances in the severe stage of the disease, with an improvement and fall in the urea/inulin clearance ratio when the serum calcium fell.

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## TREATMENT

The efficacy of treatment depends on the stage of the illness at which it is given. Some infants with hypercalcemia recover without special treatment. On the other hand, some of the severely affected infants have changes which are largely irreversible. In most cases, recovery can be accelerated by treatment. The chief methods of lowering the serum calcium are (1) a low-calcium diet, and (2) cortisone.[1-6,8,9,26-28]

A low-calcium diet is the mainstay of treatment.[9,26] This can be in the form of a low-calcium milk, produced either by treating cows' milk with a calcium-free ion exchange resin,[39,40] or as a commercial dried milk preparation, Locasol (Trufood) containing 7 mg calcium per 100 ml of reconstituted whole milk. In addition, older infants can be given a low-calcium cereal (Glaxo)—containing approximately 0.1 mg of calcium per gram of cereal. This cereal with its low-calcium content and its high inorganic phosphorus and phytate content results in an appreciable negative calcium balance due to a high content of calcium in feces.[5,9,37]

Low-calcium cereal has the added advantage of a high caloric value so that weight gain is better (and this may be an important factor in accelerating cure if calcium utilization improves). For infants who are entirely bottle fed it can be added to the milk in small amounts (up to a drachm per ounce has been found satisfactory).

The disadvantage of the low-calcium diet is that the preparation of the low-calcium milk and cereal, to be fully effective, requires the use of water of low-calcium content. In certain areas, this means distilled water.

The response of the serum calcium level to diet is not always quick and it may be desirable to give cortisone. Given orally in doses of 25 to 50 mg per day, it results in a fall in serum calcium within a few days. The effect is not permanent, as on discontinuing the cortisone, the serum calcium may rebound to a high level.[5] The main value of cortisone is its use as a short term form of therapy combined with the low-calcium diet. After two to four weeks it can be discontinued, by which time the calcium-lowering effect of the diet should be well established.[9] Used over long periods there is the risk of undesirable side effects such as hyperadrenocorticism, and masking of intercurrent infections.

The mode of action of cortisone is not understood, although its main effect appears to be in blocking absorption of calcium from the bowel. The administration of cortisone to infants with idiopathic hypercalcemia[4,5] and adults with sarcoidosis[29] results in negative calcium balances from fecal losses. Its structural similarity to vitamin D has prompted the suggestion of competition for substrate.[30]

It is important that infection should be avoided as much as possible, and if contracted, it should be promptly treated, especially if the infant is on cortisone therapy.

Other measures have been used to limit calcium absorption from the bowel. There have been no reports of phytates being used alone for the treatment of hypercalcemia in infants, but they have been used in the treatment of hypercalcemia in sarcoidosis in adults.[41] There seems to be no contraindication to their use in infants and they should increase the fecal loss of calcium if added to the low calcium diets. The disodium salt of ethylene diamine tetra acetic acid has been used as a calcium-extracting agent.[4] We believe that this treatment carries a serious risk[42] and consider it unnecessary in view of the effectiveness of other forms of treatment.

It is possible that vegetable oils containing high percentages of essential fatty acids may have some use in idiopathic hypercalcemia.

## ACKNOWLEDGMENT

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# IDIOPATHIC HYPERCALCEMIA

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## A Case Report with Assays of Vitamin D in the Serum

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IN 1952, Lightwood[1] reported a case of idiopathic hypercalcemia of infancy with failure to thrive. By October, 1956, over 200 cases had been documented, chiefly from the United Kingdom.[1-17] Relatively few reports have appeared in the United States; Deutch and Senturia[18] and Daeschner and Daeschner[19] described individual cases, and Bongiovanni *et al.*[20] reported three cases with a review of the literature. With few exceptions most infants with unexplained hypercalcemia have been receiving preparations of cow's milk with a goodly intake of vitamin D, usually more than 1,500 units/day. Many infants in the United Kingdom receive such dosage. Creery and Neill[21] reviewed the vitamin D intake of 1,087 normal infants in Belfast, Ireland, and found that 51% received between 1,000 and 2,000 units/day. Therefore, it is readily evident that the incidence of the disease among infants taking 1,000 to 2,000 units/day is quite low. The basic etiology of the disease has remained obscure, although the predominant feeling is that the condition is secondary to an exaggerated response to a moderate dosage of vitamin D.[5, 10, 22, 23]

The purpose of this paper is to report a case of prolonged hypercalcemia in which assays of vitamin D in the serum were performed.

### METHODS

The initial assay for content of vitamin D in the serum was performed by Dr. Bernard Spur of the Milk Research Laboratory of the Children's Hospital of Philadelphia. The two subsequent assays were performed by Dr. C. E. Bills, Dr. William Thomas and Dr. Gemmell Morgan utilizing the method of Bills.[24]

The methods used for analysis of blood and urine were as follows: concentration of calcium in serum was determined by the method of Harrison and Harrison;[25] concentration of phosphorus in the serum by the method of Fiske and Subbarow;[26] and that of citrate by the method of Natelson *et al.*[27] Concentration of calcium in the urine was determined by the method of Clark and Collip.[28]

### CASE REPORT

#### History

S.H. was admitted to the Harriet Lane Home at 5 years of age (September 15, 1954) with the chief complaints of unilateral facial weakness, intermittent abdominal pain, and poor weight gain.

The patient was born on July 25, 1949, of a full-term pregnancy during which the mother received supplemental calcium. The birth weight was 2,610 gm. Formula consisted of evaporated milk (400 units of vitamin D per 18 oz can). At 15 months of age homogenized milk (400 units of vitamin D per quart) was substituted for evaporated milk. The intake was about one quart daily after 2½ years of age. Supplemental water-soluble vitamin D was taken in the following dosages: 1,000 units/day until 18 months of age, 1,500 units/day from 18 months until 5 years of age, and 4,400 units/day during the month before admission. Developmentally, she sat at 7 months of age and walked and said small sentences by 2 years

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of age. From birth she had frequent vomiting, slow weight gain, anorexia, relative constipation, and frequent upper respiratory illnesses.

At 10 months of age she was first admitted to Harriet Lane Home weighing 6.65 kg. She was a slim, undernourished infant with fretful disposition and tendency to vomit.

Concentrations of calcium in the serum ranged from 12.2 to 16.2 mg/100 ml; phosphorus, 4.0 to 5.8 mg/100 ml; alkaline phosphatase, 9 to 15 Bodanski units/100 ml. The concentration of nonprotein nitrogen in the serum was 32-49 mg/100 ml and the content of carbon dioxide 23.3 mmole/l. Urinary excretion of phenolsulfonphthalein after intravenous injection was 60% in 2 hours.

An intravenous pyelogram was normal with no evidence of nephrocalcinosis. Roentgenograms of the long bones disclosed slight osteoporosis with relative increase in density of the epiphyseal plate.

During a 4-month period of hospitalization, while receiving milk and 1,000 units of vitamin D per day, she continued to vomit and was discharged weighing the same as at the time of admission.

Between 14 and 26 months of age vomiting ceased and she gained to 8.86 kg. The concentration of calcium in the serum during this period ranged from 13.7 to 16.4 mg/100 ml. She was not seen at the Harriet Lane Home from 26 months of age until 5 years of age.

At 3 years of age anorexia except for milk was a problem, and there was gradual onset of polyuria, polydipsia and occasional headaches. Three months before the second admission she became listless and intermittently complained of abdominal pain and vague pains in the extremities. Two months before admission an episode of severe abdominal pain occurred with fever and leukocytosis (30,000/mm$^3$). Because of these findings and a rigid abdomen, exploratory laparotomy was performed at another hospital. White plaques were noted over the peritoneal surfaces, which on biopsy proved to contain calcium. She remained listless and suffered from generalized pruritus. A right facial palsy developed which resolved partially before admission.

### Physical Findings

At the time of admission to the Harriet Lane Home at 5 years of age the weight was 11.5 kg, height-age of 3½ years. She was slim and undernourished with an apathetic appearance. She preferred to lie down, whimpering when disturbed. The blood pressure was 120/90 mm Hg. The skin over the abdomen and lateral aspects of the trunk showed a faint *café au lait* discoloration. There was redness of the left conjunctivae. Slit-lamp examination revealed fine crystalline deposits beneath the conjunctival basement membrane. There was brownish discoloration at the base of the teeth. Abdominal palpation disclosed variable tenderness with muscular guarding, most marked in the left upper quadrant. No mass was palpable. Pressure exerted over the wrists and knees caused pain, though no redness or swelling was discernible. There was slight facial weakness on the right.

### Laboratory Findings

In the serum the concentration of calcium was 17.1 mg/100 ml; that of phosphorus, 4.8 mg/100 ml; alkaline phosphatase, 15.4 Bodansky units; nonprotein nitrogen, 60 mg/100 ml; and total protein, 7.9 gm/100 ml. The content of carbon dioxide was 23.3 mmole/l and the concentration of citrate was 5.3 mg/100 ml (normal 2.5 mg/100 ml). The concentration of hemoglobin was 11.0 gm/100 ml with a leukocyte count of 10,700/mm$^3$. Urinalysis showed a trace of albumin, no cellular elements, maximal specific gravity of 1.014, and a 4+ Sulkowitch test for calcium. Urinary excretion of phenolsulfonphthalein was 40% in 2 hours.

### Roentgenographic Findings

Roentgenograms of the abdomen disclosed nephrocalcinosis in addition to mottled density in the perirenal areas. The intravenous pyelogram showed poor concentration with delayed clearance. Roentgenograms of the skull revealed calcification in the falx cerebri, tentorium cerebri, petroclinoid ligaments and internal carotid arteries (Fig. 1). The base of the skull did not appear abnormally dense. Roentgenograms of the long bones showed relative osteoporosis (Fig. 2) with prominent trabecular pattern, periosteal elevations along the shafts and a band of radiolucency in the subepiphyseal portion of the long bones. The epiphyseal plates appeared relatively dense.

### Initial Assay of Vitamin D

Determination of vitamin D in serum obtained in September, 1954, was performed by

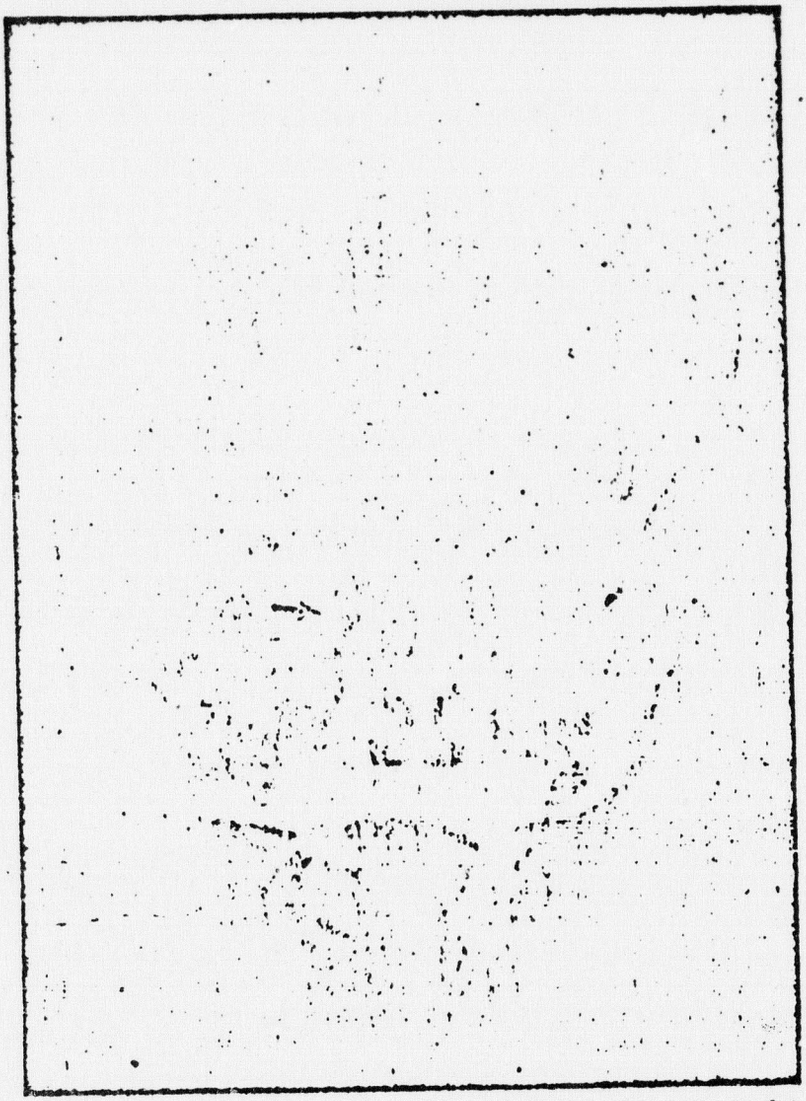

FIG. 1A. Anteroposterior projection showing calcification in the falx cerebri and the carotid arteries (arrow).

Dr. Bernard Spur, Director of the Milk Research Laboratory of the Children's Hospital of Philadelphia, and showed a concentration of 23 units of vitamin D per milliliter of plasma, as compared to a normal value of 0.60-1.65 units/ml noted by Warkany and Mahon.[29] Because of an insufficient amount of serum, this test was performed on only four rachitic rats instead of the usual 8 or 10 animals. The result must therefore be taken with some reservation.

### Course (Fig. 3)

EXCRETION OF CALCIUM IN URINE: During the hospitalization of 2 months the patient was weak, listless and complained of occasional pain in the abdomen and extremities. Initially, while receiving a milk diet, the 24-hour excretion of calcium in the urine was 135 mg. After 2 weeks of receiving a milk-free diet, the 24-hour urinary excretion of calcium on two occasions was less than 40 mg.

HYPERCALCEMIC "CRISIS": On September 23, after 24 hours of poor fluid intake, she complained of severe abdominal pain; the abdomen was noted to be rigid, the leukocyte count was 30,000/mm³ and the blood pressure rose from 128/90 to 210/160 mm Hg. She vomited blood-stained material, had a generalized con-

FIG. 1B. Lateral projection showing calcification of petroclinoid ligament. The base of the skull does not appear sclerotic.

vulsion, and lapsed into coma. The concentration of calcium in the serum was 16.0 mg/100 ml, and that of phosphorus was 6.8 mg/100 ml. Sodium EDTA* (sodium Versenate®) was given intravenously, 200 mg over the first hour and 800 mg over the next 16 hours. Within 30 minutes she regained consciousness and 6 hours thereafter was able to retain fluids orally. After 8 hours of therapy the oxalate-precipitable calcium in the serum was 12.8 mg/100 ml, with a total ashed calcium of 15.7 mg/100 ml.

Subsequently, the blood pressure remained elevated between 130/90 and 210/160 mm Hg, being usually 160/110. There was no response to administration of Raudixin® or intramuscular administration of magnesium sulfate. The concentration of non-protein nitrogen remained elevated between 35 and 60 mg/100 ml.

In order to exclude the possibility of parathyroid adenoma, an exploration of the neck and anterior portion of the mediastinum was performed and no adenoma was found.

On October 1, the patient had a second "crisis," though symptomatically not as severe as the first. On this occasion the concentration of calcium in the serum was 18.2 mg/100 ml. She was again given sodium Versenate® intravenously with improvement.

CORTISONE THERAPY: On October 2, oral administration of cortisone, 100 mg/day, was begun with a gratifying fall in the concentration of calcium. Before cortisone therapy, the concentration of calcium was 14.7 to 18.2 mg/100 ml, and the alkaline phosphatase activity was

* Sodium ethylenediaminetetraacetate.

Lamb soup "recipe":"
1½ cups strained lamb (prepared baby food)
2½ tbs. sugar
½ tsp. salt
2 tsp. olive oil
2½ tbs. rice flour
32 oz. water

FIG. 2A. Roentgenogram at 11 months of age (June 1950) showing slight osteoporosis and relative density of the epiphyseal lines.

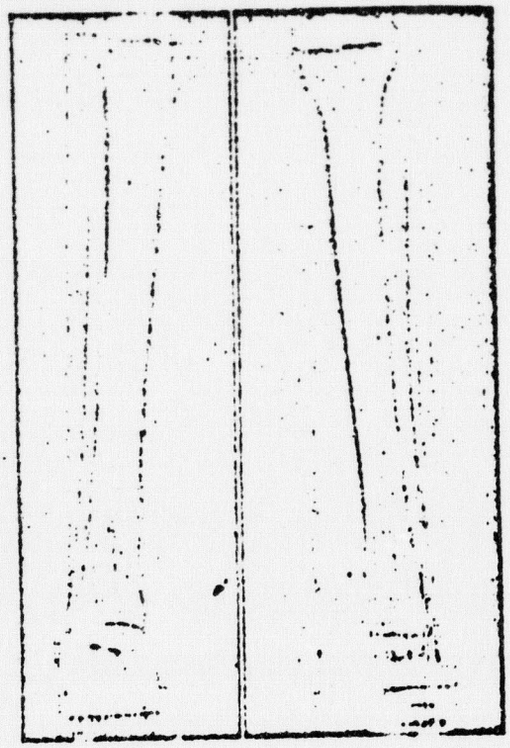

FIG. 2B. Roentgenogram at 5⅓ years (September 1954) (second admission to the hospital) showing relative osteoporosis with prominent trabecular pattern, periosteal elevations along the shafts, relative density of the epiphyses, and a band of radiolucency in the subepiphyseal area.

12.0 to 17.3 Bodansky units; the concentration of citrate in the serum was 5.3 mg/100 ml. While receiving cortisone therapy the concentration of calcium in the serum was 11.8 to 13.7 mg/100 ml and the alkaline phosphatase activity was 3.2 to 11.1 Bodansky units. The concentration of citrate dropped to levels of 1.8 and 2.8 mg/100 ml. She continued to refuse most foods other than milk, which she was allowed to take. While on this regimen the 24-hour urinary excretion of calcium was less than 40 mg/24 hours on two occasions.

On November 3, 1954, multiple petechiae were noted over the lower extremities but these disappeared in 3 days; the platelet count was 388,000/mm³.

The dosage of cortisone was gradually decreased and, finally, administration was discontinued. On November 11, she was discharged from the hospital with a mandatory fluid intake of 1,000 ml/day, with milk as desired. No vitamin D was given after admission or subsequently.

Five days after administration of cortisone was discontinued, the concentration of calcium in the serum had risen to 14.6 mg/100 ml, and after 2½ weeks it was 16.4 mg/100 ml. On November 30, the oral administration of 25 mg of cortisone daily was again begun and the concentration of calcium in the serum fell to 13.4 mg/100 ml. In January 1955, the dosage of cortisone was reduced to 12.5 mg/day, and 3 months later the concentration of calcium had risen to 15.6 mg/100 ml. Henceforth, 18.5 mg of cortisone was given per day until November 1955. The dosage of cortisone was then gradually reduced and administration was discontinued without a subsequent rise in concentration of calcium in the serum.

At the time of discharge from the hospital a firm abdominal mass was palpable in the left upper quadrant. This enlarged further during the subsequent week and was associated with moderate pain. Roentgenograms of the abdomen disclosed a mottled radio-opaque mass in the left upper quadrant. One month later the mass was no longer palpable, nor was it demonstrable by roentgenograms. This was presumed to be spleen which became infarcted and receded, with probable atrophy.

LOW CALCIUM DIETS: In February 1955, because of persistent hypercalcemia while receiving cortisone and ad libitum ingestion of milk, she was given a diet low in calcium with elimi-

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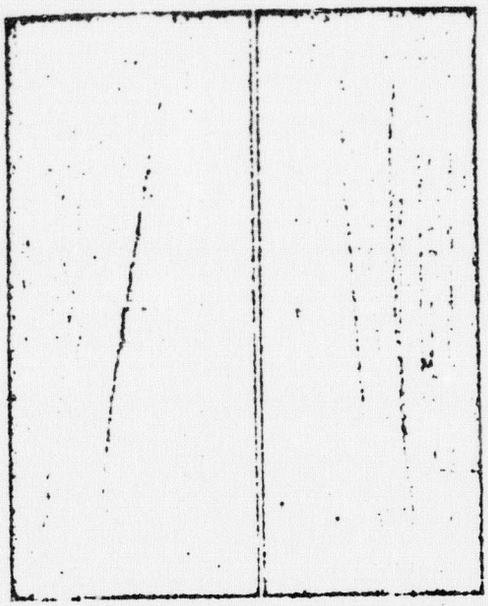

FIG. 2C. Roentgenogram at 5½ years (March 1955) discloses increase in the width of the subepiphyseal rarefaction with minute trabecular fractures noted at the ends of the long bones. The relative density of the epiphyses is again noted.

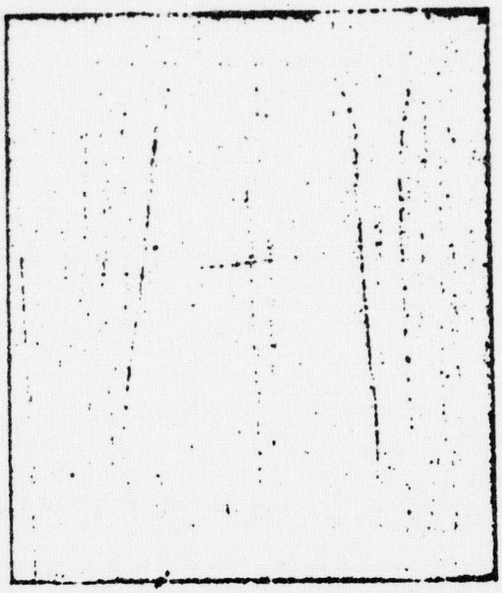

FIG. 2D. Roentgenogram at 6½ years (February 1956) discloses re-mineralization of the radiolucent areas with healing of the minute trabecular fractures, calcification in the periosteal elevations, and decrease in the relative density of the epiphyses.

nation of foods of high-calcium content and substitution of a "lamb soup"* for milk. In spite of the unpleasant taste of the lamb soup, she took 600 ml/day, which contained 27 mg of calcium. The total daily diet was analyzed on two occasions and contained 58 mg/day and 80 mg/day of calcium, respectively.

From the time the diet low in calcium was introduced there was gradual and remarkable improvement in personality and activity. From a listless, fretful child she became active and pleasant.

CONCENTRATION OF VITAMIN D IN SERUM: Six months after admission and discontinuation of administration of vitamin D, a vitamin D assay of serum revealed a level of 5 units/ml, which is above the normal of 1 ± 0.5 units/ml. A vitamin D assay performed in June 1956 revealed a vitamin D level in the serum of 2.0 units/ml. This was after 21 months of a regimen without added vitamin D.

CITRATE THERAPY: The concentration of calcium in the serum continued to be at the upper limits of normal in spite of the low intake of calcium, and the urinary excretion of calcium was high (108 to 208 mg/24 hr). In September 1955, in an effort to reduce the hypercalciuria, she was given Poly Citra® (molar sodium and potassium citrate),* 45 ml/day. After 6 weeks, the dosage was reduced to 20 ml/day because of alkalosis. With this therapy the urinary excretion of calcium fell from 108 to 37.5 mg/24 hours. Balance studies revealed a negative calcium balance of −94 mg/day just before citrate therapy and −23 mg/day after 6 weeks of citrate therapy. The concentration of calcium in the serum was 11.4 mg/100 ml at the onset of citrate therapy and 11.1 mg/100 ml after 6 weeks. During citrate therapy the concentration of citrate in the serum was high, ranging from 6.2 to 8.3 mg/100 ml.

In February 1956 the concentration of calcium in the serum was 12.0 mg/100 ml and an additional 100 mg of calcium was given in the diet in the form of calcium lactate, 700 mg/day. After February 1956, the concentration of calcium in the serum remained between 10.9 and 12.0 mg/100 ml and the intake of calcium

* See recipe in footnote on page 261.

* Supplied by the Willen Drug Co., Baltimore, Maryland. This preparation supplies 1 meq each of sodium and potassium/ml.

FIG. 3. *Course from September 1954 through June 1957.* The numbers at the top of the diagram indicate the following events: 1) Hypercalcemic "crisis" treated with 1 gram of sodium Versenate® intravenously over a 16-hour period. 2) Surgical exploration of the neck and anterior mediastinum revealed no parathyroid adenoma. 3) Second hypercalcemic "crisis" treated with sodium Versenate® intravenously. 4) Discharge from hospital. 5) Beginning of clinical improvement. Note: The dotted areas indicate the normal range for calcium and phosphorus. The citrate therapy is molar sodium and potassium citrate (Poly Citra®), courtesy of the Willen Drug Company, Baltimore, Md.

is molar sodium and potassium citrate (Poly Citra®), courtesy of the Willen Drug Company, Baltimore, Md.

was gradually increased to 530 mg of calcium/day in April 1956. The urinary output of calcium remained low. A balance study done in June 1956 disclosed a positive calcium balance of 152 mg/24 hours. Roentgenograms of the abdomen and skull made in July 1956 revealed no evident change in soft tissue calcification.

In July 1956, the citrate therapy was discontinued with no rise in concentration of calcium in the serum, but a rise in the urinary excretion of calcium did occur from 47 mg/24 hours to 121 mg/24 hours 1 month later. The concentration of citrate in the serum fell from 8.0 to 2.8 mg/100 ml.

Between July 1956 and December 1957 the concentration of calcium in the serum varied between 10.5 and 11.5 mg/100 ml. Urinary excretion of calcium in November 1956 was 65 mg/24 hours and in May 1957, 80 mg/24 hours. During this period the concentration of phosphorus in the serum gradually fell from 5.2 mg/100 ml in September 1956 to 3.2 mg/100 ml in January 1957, and in May 1957 was 5.0 mg/100 ml. The alkaline phosphatase activity remained constant between 15 and 20 Bodansky units. The dietary intake of calcium was gradually increased until in May 1957 she was taking 480 ml of milk daily, and either cheese or ice cream daily.

ROENTGENOGRAMS OF LONG BONES: In March 1955, while the patient was receiving a diet low in calcium and 12.5 mg/day of cortisone orally, roentgenograms of the long bones showed a further progression of the pathologic findings. The bands of subepiphyseal rarefaction had become wider with minute trabecular fractures noted at the ends of several of the long bones (Fig. 2C). This picture was practically the same in July 1955. In September 1955, when the patient was in negative calcium balance, roentgenograms disclosed remineralization of the subepiphyseal areas of radiolucency at the ends of the long bones with healing of the minute trabecular fractures. Further evidence of improvement was noted in roentgenograms made in February 1956 (Fig. 2D). Osteoporosis of the shaft had become less in degree while the relative density of the epiphyses had become less marked. Roentgenograms made in July 1956 disclosed normal bone structure.

HYPERTENSION AND RENAL FUNCTION: The blood pressure had been persistently elevated to 160/100 mm Hg or higher until January 1956 when it began to fall and in March 1956 the blood pressure was 100/70 mm Hg.

Study of renal function disclosed that the concentration of nonprotein nitrogen in the serum remained elevated between 40 and 48 mg/100 ml. In January 1956, the urea clearance was 28% of normal, excretion of phenolsulfonphthalein was 37.5% in 2 hours, and the maximal specific gravity was 1.014. Urinalysis was normal. Urea clearance in January 1957 was 43% and excretion of phenolsulfonphthalein was 48% in 2 hours, suggesting some improvement of renal function. Specific gravity, however, remained fixed at 1.010.

GROWTH: Until December 1955 growth in height had been relatively slow; however, during the next 3 months she grew 4.5 cm and during the next year, 11 cm (Fig. 4).

NEUROLOGIC CHANGES: During the study the patient displayed evidence of nervous system damage. The partial right facial palsy which was present at the time of admission resolved in 2 weeks time. On October 25, 1954, a generalized convulsion was followed by intermit-

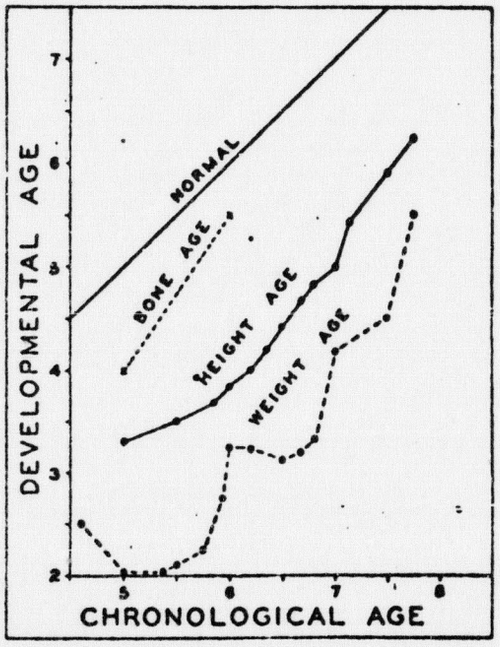


FIG. 4. Developmental curve illustrating advancement in height, weight and bone age during the period of treatment. (Height and weight standards from Wilkins, L.: The Diagnosis and Treatment of Endocrine Disorders in Childhood and Adolescence, 1st Ed. Springfield, Thomas, 1950.)

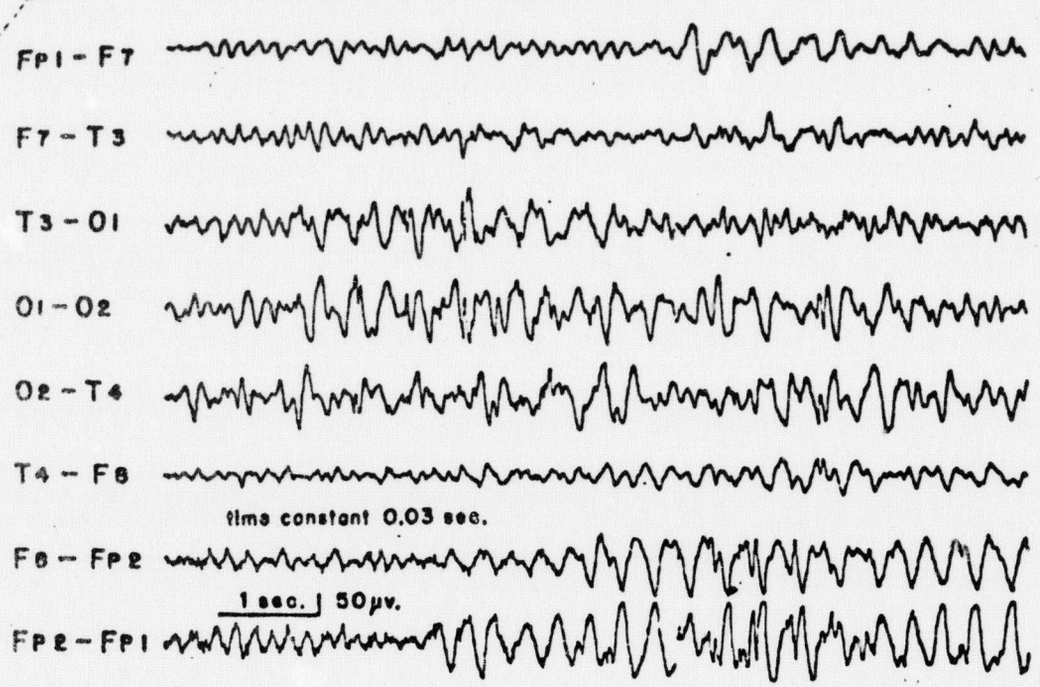


FIG. 5. Electroencephalogram made in June 1956 showing three independent foci or spikes associated with slow waves in left occiput (01), right occiput (02), and right pre-frontal (Fp2). Electrode labeling is International Standard. J.H.H. EEG #10705.

tent twitching of the right eyebrow and right hand for 3 days. She continued to have seizures characterized by aphonia and gradual loss of contact to the point of coma. These occurred at intervals of from 3 days to 1 month until December 1955. Five such episodes were observed during which the concentration of calcium in the serum was not elevated above the nonseizure levels. In August 1956, administration of diphenylhydantoin (Dilantin®) was begun and since then no seizures have occurred. An electroencephalogram in June 1956 was grossly abnormal with independent foci of spikes with slow waves (Fig. 5).

At times there was apparent hearing impairment. Evaluation disclosed normal reception but inability to perceive sound accurately, indicating a central inability to interpret sound.

In April 1956, a Wechsler Intelligence Test disclosed a verbal intelligence quotient (I.Q.) of 67, and a nonverbal I.Q. of 74; full I.Q. 67. It was again noted that she had difficulty deciphering the spoken word.

## DISCUSSION

The patient manifested a clinical picture of unexplained mild idiopathic hypercalcemia of infancy at 10 months of age. No therapeutic measures were taken at this time to correct the hypercalcemia, and when hospitalized at 5 years of age symptoms of severe idiopathic hypercalcemia were evident. However, this patient differs in certain respects from other patients with severe idiopathic hypercalcemia. She does not show either the elfin facies or the osteosclerosis described by Schlesinger *et al.*[13] in a review of 10 cases.

The daily supplementation of vitamin D which the patient received would not normally be considered a toxic dosage, but the initial concentration of vitamin D in the serum was elevated (23 units/ml of serum) and only gradually fell to within normal limits 21 months after administration of vitamin D was discontinued, at the time when the concentration of calcium in the serum became normal.

The osseous findings in this case are of considerable interest since evidence of demineralization of bone was seen. Roentgenograms showed subepiphyseal rarefac-

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tion, periosteal elevations, and relative rarefaction of the shafts of the long bones as compared to the epiphyses. These changes are similar to those described by Ross[11] and Debre[12] in cases of vitamin D intoxication in children. However, roentgenograms in this case did not show the marked increased density at the epiphyseal plate which is usually noted in both vitamin D intoxication and idiopathic hypercalcemia. Certain experimental findings are of interest in an attempt to understand the bone picture displayed by this patient. Harris and Innes[13] found that high doses of irradiated ergosterol given to rats initially resulted in increased deposition of calcium in the bone, particularly at the epiphyseal line. With prolonged therapy, demineralization occurred with resorption of the subepiphyseal spongiosa. With time they noted that the renal excretion of calcium increased, resulting in negative calcium balance. The demineralization is probably a direct effect of vitamin D on the bone tissue and it is possible that the demineralization of the bone in the patient studied by us was due to a prolonged cumulative effect of vitamin D. As hypercalcemia improved, remineralization took place, even in the face of negative calcium balance. The source of calcium for remineralization was therefore endogenous, either from soft tissue deposits or from redistribution in the bone itself. The latter possibility seems more likely since there was no evident decrease in roentgenographic evidence of soft tissue calcification at the time of remineralization. It is felt that the unusual duration of the disease fostered the changes of demineralization. Hypercalciuria may have acted as a safety valve to allow the disease to persist so long before severe symptoms of hypercalcemia were present.

In addition it should be emphasized that the patient has now been followed for 2 years since the concentration of calcium in the serum returned to normal (3½ years in all). During this period she has received a full diet with 480 ml of milk and no added vitamin D, and on this regimen has been normocalcemic with a normal rate of growth. Though not conclusive, this follow-up does not implicate any other factor as a cause for hypercalcemia in the absence of supplemental vitamin D.

The fall in the concentration of phosphorus in the serum noted in this patient during convalescence is of interest. Howard and Meyer[31] reported a low concentration of phosphorus in the serum during the convalescent period in adults with vitamin D intoxication.

The concentration of citrate in the serum was initially elevated, a finding which Harrison[33] observed in hypervitaminosis D. He noted that elevated citrate levels have been found in a variety of conditions in which demineralization of the skeleton and hypercalcemia occur. Winberg and Zetterström[16] reported a low concentration of citrate in the serum in hypervitaminosis D, and Forfar and associates[12] noted a low concentration in idiopathic hypercalcemia, but too few determinations have been made in such patients to permit any conclusions concerning the significance of citrate levels in hypercalcemic states. The subsequent citrate levels disclosed low to normal values during cortisone therapy, high values during citrate therapy, and normal values after administration of citrate was discontinued and osseous healing had occurred.

The fundamental reason why idiopathic hypercalcemia should occur in infants receiving moderate dosage of vitamin D is not settled. There could be a physiologic difference in the response to vitamin D. Follis *et al.*[37] have stated that there is a wide variability in the vitamin D requirements in infancy. A second possibility is a metabolic defect in the degradation mechanism of vitamin D such that excessive accumulation of the vitamin could occur. In this regard Fyfe[38] demonstrated high concentrations of vitamin A in the serum with a greater than normal rise after oral administration of vitamine A to patients with idiopathic hypercalcemia of infancy. He suggested that there might be a concomitant defect in the metabolic handling of vitamin D. Fellers and

Schwartz[39] have reported studies of concentrations of vitamin D in the plasma of two infants with hypercalcemia, osteosclerosis, and mental and physical retardation. Both of these infants had high concentration of vitamin D in the serum. The levels were comparable to those found in two children who were given 100,000 units/day of the vitamin. This suggests some abnormality in the vitamin D metabolism of hypercalcemic infants. The assays of vitamin D in the serum of the patient studied by us also suggest failure of normal metabolism of vitamin D. On the other hand, Morgan and co-workers[40] have recently obtained vitamin D assays in the serum of two patients with idiopathic hypercalcemia in infancy. The results, performed by the same laboratory as the latter two determinations in the patient studied by us, were within normal limits. The paucity of determinations of concentrations of vitamin D in the serum of infants with hypercalcemia and the discrepant results reported prevent any conclusions from being made concerning the fundamental metabolic disturbance.

Whether the role of vitamin D is primary or secondary, it appears to have been contributory as a cause of the hypercalcemia in this particular case. Since a daily intake of 400 units of vitamin D has been shown to be adequate for normal growth and prevention of rickets in infancy,[41] it would seem advisable to limit the prophylactic vitamin D doses to this level rather than incur the danger of hypercalcemia on higher dosage, rare though it may be.

Clinically, several points are worthy of note. The retardation in growth rate persisted throughout the period of hypercalcemia. When the concentration of calcium in the serum returned to normal and the osseous abnormalities improved, an accelerated growth spurt occurred, followed by a normal rate of growth (Fig. 4). The hypertension gradually resolved, with normal blood pressure being obtained when the concentration of calcium in the serum returned to normal. Other effects of hypercalcemia left permanent residua. Renal function showed only slight improvement. Personality function and seizure frequency improved with time but the intelligence defect and perceptive hearing defect showed no appreciable improvement.

## SUMMARY

A case of idiopathic hypercalcemia present from early infancy and diagnosed at 5 years of age is reported in which the serum assay of vitamin D indicated elevated levels. After discontinuation of supplemental vitamin D and a diet low in calcium the concentrations of calcium and vitamin D in the serum gradually returned to normal over a period of 18 months. Roentgenograms of the bones showed evidence of demineralization rather than increased density as reported in other cases of "idiopathic" hypercalcemia. During a subsequent 2-year follow-up the patient has maintained a normal serum calcium. The etiology is discussed with particular reference to the role of vitamin D in this case.

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# HYPERVITAMINOSIS D WITH OSTEOSCLEROSIS

E495

BY

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Administration of vitamin D in high dosage produces extraosseous calcification, renal failure and usually hypercalcaemia, with a characteristic set of symptoms (Jeans, 1950). Its effects on bone have been alluded to in a number of publications (Jeans, 1950; Ross, 1952; Debré, 1948; Anning, Dawson, Dolby and Ingram, 1948; Ross and Williams, 1939; Tumulty and Howard, 1942; Danowski, Winkler and Peters, 1945; Howard and Meyer, 1948; Freeman, Rhoads and Yeager, 1946; Thatcher, 1931). In adults the characteristic roentgenologic bone finding is rarefaction. In children rarefaction is also reported, but with the additional finding of increased density of the zone of provisional calcification, and periosteal thickening (Ross, 1952).

The following case report demonstrates that excess ingestion of vitamin D may be accompanied by a severe degree of osteosclerosis, which is reversible, in addition to its better known effects.

## Case History

A 5½-year-old white boy was admitted to the Orthopaedic Hospital Clinic complaining of pain in the right leg and flat feet. At the age of 3 he was considered elsewhere to have rickets on the basis of a 'peculiar feeling to the bones of the skull' and radiographs of the wrists. He was given two capsules of vitamin D daily, each containing 50,000 units, in addition to two tablespoons or more of cod liver oil and multivitamin drops. A few months after this he developed nausea and non-tender recurrent lumps the size of half a lemon, over both tibias. His physician prescribed vitamin C and the lumps disappeared. In addition to the vitamin therapy at home, he was given a teaspoonful of cod liver oil daily at nursery school. After nine months of this therapy he became irritable, restless and nauseated, and the vitamins were stopped by the family. At the age of 4½, a diagnosis of rheumatic fever and anaemia was made and treatment was started with ferrous sulphate and sodium salicylate. His appetite was good, but he continued to be irritable and restless, sleeping only five hours at night. During the ensuing year his refusal to participate in school activities was ascribed by his teacher to stiffness in the extremities.

His birth weight was 8 lb. 8 oz. He was the son of a young woman who was married and separated before the child was born. Labour and delivery were normal. He was breast fed for eight months. He sat at 5 months, stood at 10 months, and walked at 11 months. His first tooth erupted at 4 months.

He was brought up chiefly by the mother's parents, while the mother worked. At an early age he had a tonsillectomy, adenoidectomy and circumcision. He also had measles.

Physical examination revealed an alert, hyperactive, well-developed and nourished white boy (Fig. 1). There was increased A-P diameter of the head with a suggestion of frontal and parietal bossing. The eyes, ears, nose and throat were normal. Dentition was normal, and the teeth appeared healthy. The thyroid gland was not

FIG. 1.—The patient at 5½ years of age.

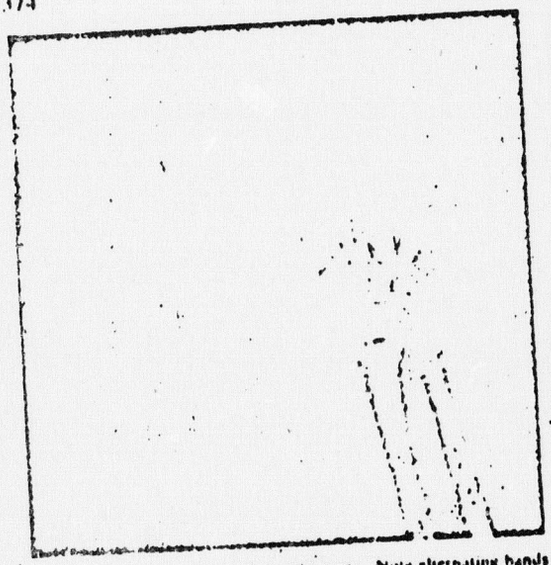

FIG. 2.—Radiograph at initial examination. Note alternating bands of decreased and increased density at ends of radius and ulna.

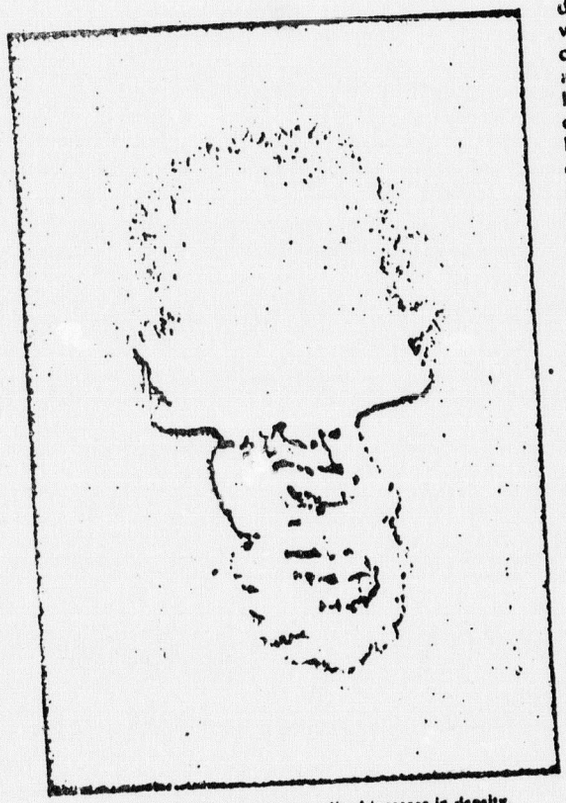

FIG. 3.—Skull showing generalized increase in density.

palpable. The thorax showed beading of costochondral junctions. The heart, lungs and abdomen showed no abnormalities. The genitalia were normal for a boy of 5. The testes were in the scrotum.

The epiphyseal regions of the long bones were stocky and broad. There was no tenderness or pain. There was eversion of the os calcis and loss of the longitudinal arch bilaterally. There was some spasm of the left rectus femoris muscle and 20-degree flexion contractures of the knees. The skin was clear. There were no palpable calcific deposits anywhere. There was a healed ecchymosis on the lateral aspect of the right thigh.

A complete blood count showed 3·70 million erythrocytes, 12·8 g. haemoglobin, 10,400 leucocytes, with 40% polymorphs, 52% lymphocytes, 4% eosinophils, and 4% transitional forms. Urine analysis showed pale yellow urine of specific gravity 1,005, acid reaction, no sugar, acetone, albumin or formed elements. Urine calcium was 0·19 g. in a 24-hour volume of 1,750 ml. Serum calcium was 17 mg. per 100 ml., phosphorus 5·2 mg. per 100 ml., alkaline phosphatase 19 King-Armstrong units, acid phosphatase 5·3 King-Armstrong units, and protein-bound iodine 6·8 µg. %. Radiographs showed generalized increase in density of the bones. Alternating bands of decreased and increased density were present in the metaphyses, best seen at the wrist (Fig. 2). The cortices of the metatarsals, metacarpals, and phalanges were thickened. Metaphyseal areas were a little wider than usual and remodelling had not proceeded normally. There was some encroachment on the medullary canals at the ends of the long bones and in the shaft, caused possibly by thickened cortex. The base of the skull and cranial vault were increased in density (Fig. 3). The petroclinoid ligaments were heavily calcified. Periarticular calcifications were present about the feet, hips, hands, ankles and shoulders. Kidney shadows were dense but not markedly so. The lumbar spine showed dense and square appearing vertebral bodies (Fig. 4). Intervertebral discs were not calcified. Soft tissue calcification or periosteal new bone could be made out along the sternum.

A chest film made two years previously showed no abnormalities in the lung fields, and normal bone density. Films of the wrists and skull made one and a half years previously showed normal bone density (Figs. 5-6). Zones of provisional calcification were maintained. The epiphyseal lines were not widened. Bony maturation corresponded satisfactorily with the given chronological age of 4 years. The skull showed no abnormalities. There was no roentgen evidence of rickets.

The family was instructed to stop administering vitamin D and presumably did so. They did not return for follow-up observation and care except sporadically, as he was under private care for general paediatric supervision.

Radiographs were obtained at seven, eight and 10 months after initial examination. An antero-posterior view of the pelvis after seven months showed a thin zone of decreased density about the pelvic bones, probably representing new growth (Fig. 7). Femoral

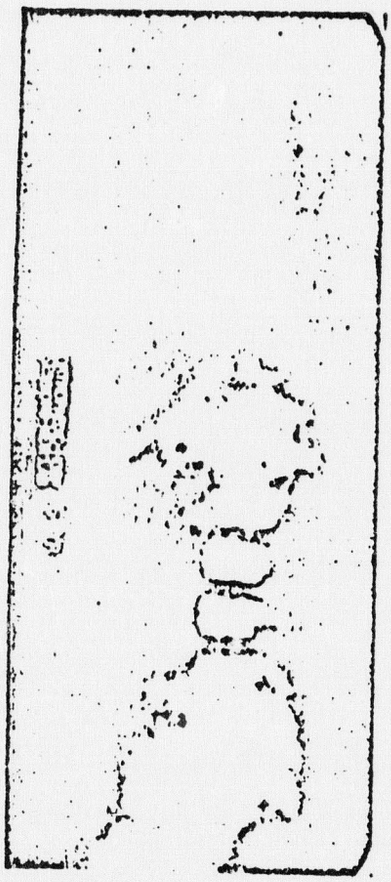

FIG. 4. Note the dense square-appearing vertebral bodies

FIG. 5. Normal appearing bone structure at the age of 4.

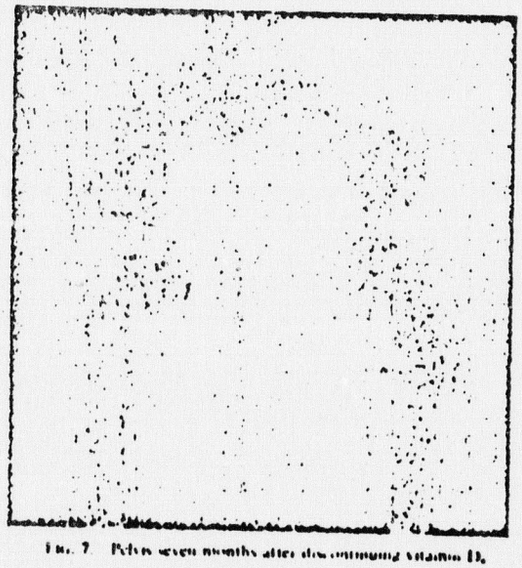

FIG. 7. Pelvis seven months after discontinuing vitamin D.

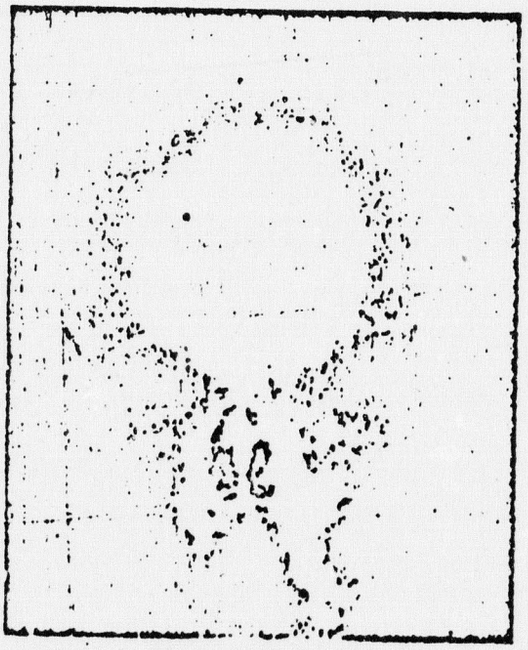

FIG. 6. Normal appearing skull at the age of 4

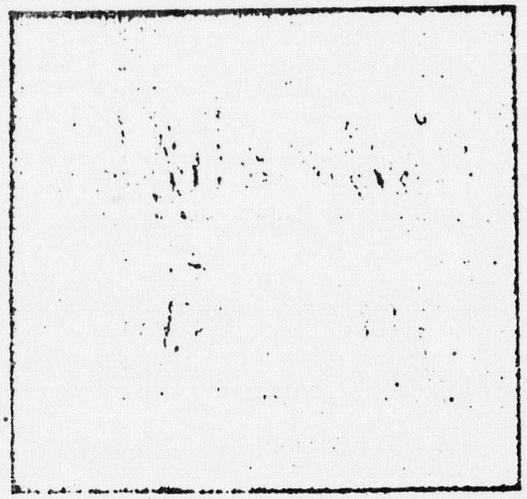

FIG. 8.—Note new bone growth at ends of radius and ulna.

arteries were seen to be delicately outlined by calcium. A month later, films of the wrists showed widened zones of relatively decreased density about the ends of the long bones, presumably representing bone laid down since the patient was taken off massive doses of vitamin (Fig. 8). Periarticular calcification persisted. Bony maturation was about 4 years, definitely retarded for the chronologic age of 6 years and 2 months. Two months later zones of lessened density were seen about the metaphyses adjacent to the knees and ankles (Fig. 9a).

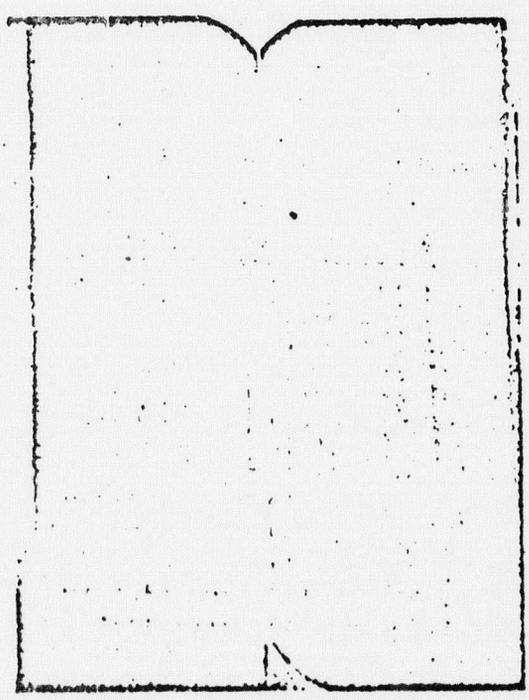

FIG. 9a.—Lower extremities at 5 years.

Fifteen months after our first examination, he was taken to his private paediatrician, who kindly provided us with data concerning his course during the next several months. He was kept in hospital at this time because of fever, swelling of face and abdomen, and haematuria, after an upper respiratory infection. He had slight fever, tachycardia, a blood pressure of 180/120 mm. Hg, and moderate oedema of face and abdomen. Treatment was instituted with strict bed rest, penicillin and moderate salt restriction. Parenteral reserpine and 'apresoline' (hydrallazine) were given for one week, with a drop in blood pressure to 130/85 mm. Hg. An intercurrent viral gastro-enteritis was followed by loss of facial oedema and ascites. Blood pressure remained between 130/90 and 110/80 mm. Hg without further hypotensive drugs. His weight had dropped to 40 lb. from 48·5 lb. on admission. His urine which had many red cells on admission, cleared to 20-25 per h.p.f. and he was discharged home.

Radiographs during this period revealed bone density to be less than previously. Calcifications were present in the falx cerebri and tentorium. Periarticular calcifications were still evident about the hips. The transverse diameter of the heart was at the upper limit of normal. Renal shadows were moderately dense. The tip of the 12th rib was apparently fractured. Bony maturation was about 4 years, compared with the chronological age of 6 years and 10 months.

Laboratory studies during this period and for the next several months are tabulated (Table I). The blood pressure remained near 120/90 mm. Hg on hypotensive therapy. The urine continued to show albumin, red blood cells and casts. The blood sedimentation rate and non-protein nitrogen remained elevated.

The family did not follow the rigid routine of bed rest prescribed, and sent him to school without medical permission.

When he was seen by the author one year after being in hospital under Dr. Woltmann, he was an alert, 7-year-old boy with a uraemic odour and marked pallor. Blood pressure was 190/130 mm. Hg. The fundus showed moderate crossing changes but no haemorrhages or papilloedema. Lungs were clear. The heart was enlarged to percussion and had loud tones of poor quality. There was a late diastolic sound suggestive of a presystolic murmur. The abdomen showed no abnormalities. There was no ascites or oedema. Skeletal survey by radiograph at this time showed continued loss of bone density (Fig. 9b). Bone of more normal density had been laid down since vitamin dosage had been discontinued. The overall decrease in density had been spectacular. Soft tissue calcifications were still demonstrated in the tissues about the hips. Chest film showed the heart to be moderately enlarged. The renal shadows had decreased in size and were increased in

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TABLE 1
LABORATORY FINDINGS DURING 1957

| Date (1957) | Urinalysis | Haemoglobin (g./100 ml.) | Non-protein Nitrogen (mg./100 ml.) | Sedimentation Rate (mm./hr.) (Wintrobe) |
|---|---|---|---|---|
| February 28 | 4+ albumin; 10-13 R.B.C.; 3-4 W.B.C.; many casts | 12 | 76 | 40 |
| March 28 | 4+ albumin; 12-15 R.B.C.; 10-14 W.B.C.; many casts | 13·4 | 76 | 44 |
| May 16 | 3+ albumin; 8-10 R.B.C.; 10-12 W.B.C.; granular casts | 13·4 | 72 | 39 |
| September 12 | 4+ albumin; 6-8 R.B.C.; 10-12 W.B.C.; granular casts | 10·7 | 103 | 92 |

density, although no definite calcifications were identified.

An electrocardiogram was within normal limits. Blood studies and urine analysis are tabulated (Table 2). A grave prognosis was given and a low protein diet omitting milk was advised. In spite of this, however, the family insisted he attend school if at all possible. The next few weeks saw development of widespread ecchymosis, oozing of blood from the nose, and increased depth of breathing with gallop rhythm. The family called in a physician living near them, who supervised his home care. He died soon after being readmitted to hospital.

**Autopsy.** Autopsy revealed small amounts of fluid in the peritoneal and pericardial cavities. The heart weighed 268 g. The left ventricle measured 14 mm. in thickness. There were some atherosclerotic changes in the first part of the aorta. The coronary ostia were patent. Both lungs were dark red and firm posteriorly, appearing juicy, bloody, and mucopurulent on cut section. The gastrointestinal tract showed haemorrhagic spots in the stomach and first portion of the duodenum. There was an intestinal intussusception about 6·5 cm. in length, approximately 90 cm. above the ileocaecal valve. The liver was abnormally heavy at 850 g. Cut surface showed fatty change. The spleen, pancreas and adrenals were normal.

Both kidneys were embedded in a small amount of fat. The right kidney weighed 47 g. (normal 74 g.) and the left kidney weighed 53 g. (normal 75 g.). On cut surface the capsule stripped with difficulty. After removal of the capsule the surface of both kidneys appeared granular. The pelvis appeared normal.

Lymphoid tissue was grossly normal. The thyroid showed cystic change. The parathyroid glands appeared normal. The bone marrow was deep red-brown in

TABLE 2
TERMINAL LABORATORY STUDIES

| Laboratory Studies | Findings |
|---|---|
| Urinalysis | Sp. gr. 1,012, pH 6·0, albumin 4+; sugar negative, 15-25 W.B.C., 4-6 R.B.C., occasional epithelial cell, occasional broad coarse casts, occasional coarse granular cast, occasional broad W.B.C. cast |
| Complete blood count | Hb 5·9 g./100 ml., W.B.C. 10,900; polymorphs 65, lymphocytes 22, basophils 1, monocytes 9, eosinophils 3, haematocrit 18% |
| Serum creatinine | 6·1 mg./100 ml. |
| Blood urea nitrogen | 108 mg./100 ml. |
| Serum K | 4·7 mEq/litre |
| Serum alkaline phosphatase | 8·0 Bodansky units |
| Serum inorganic phosphorus | 9·2 mg./100 ml. (5·3 mEq/litre) |
| Serum calcium | 8·4 mg./100 ml. (4·1 mEq/litre) |

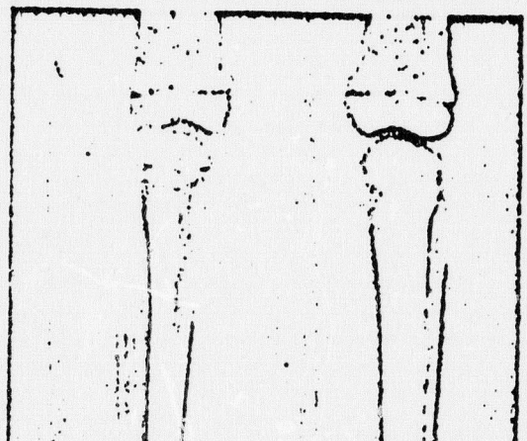

FIG. 9b.—Lower extremities at 7½ years, showing course of sclerotic bony process.

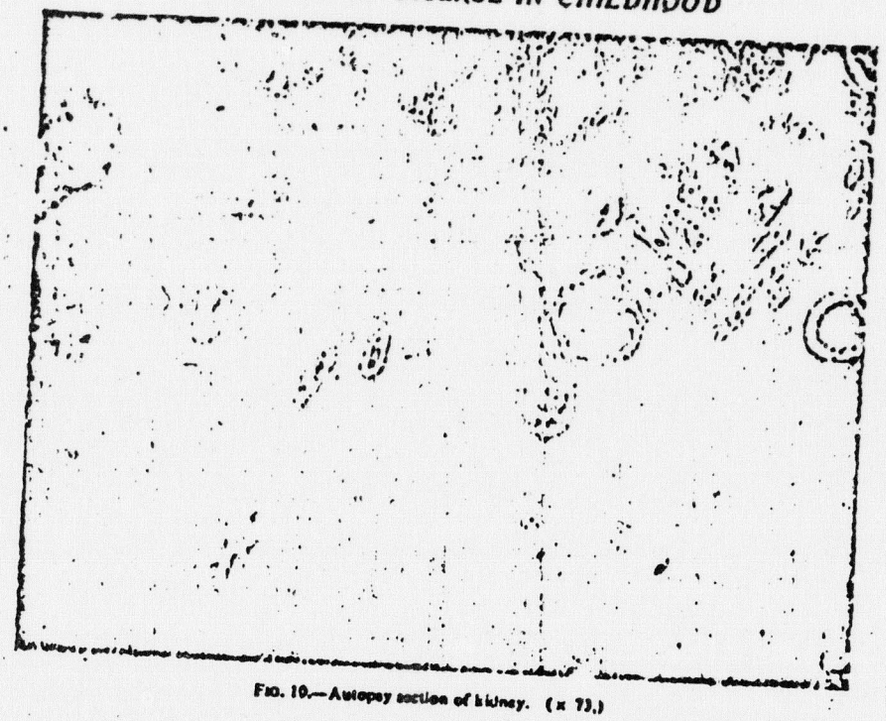

FIG. 10.—Autopsy section of kidney. (x 73.)

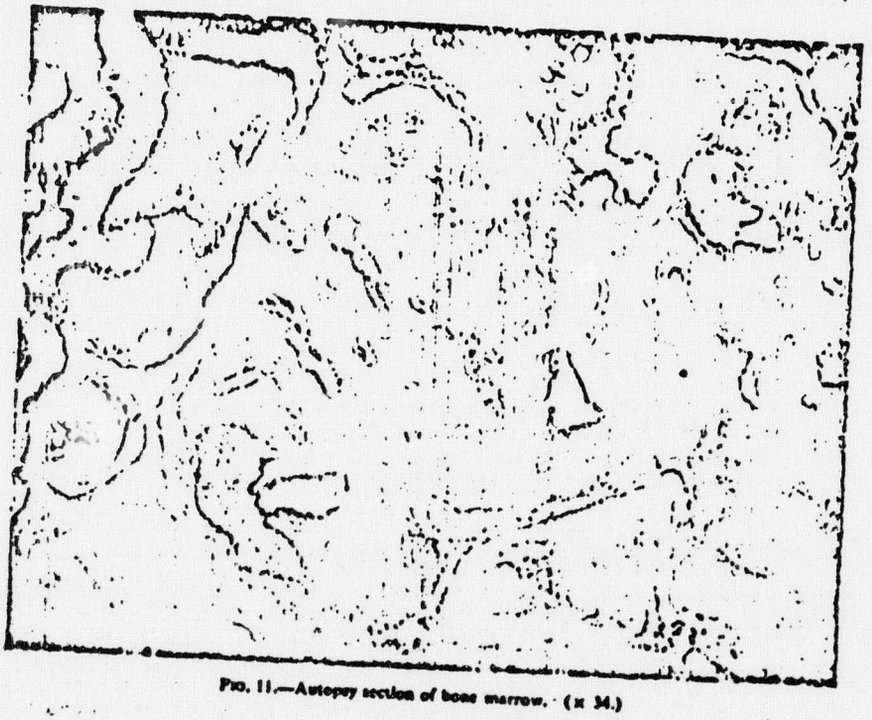

FIG. 11.—Autopsy section of bone marrow. (x 34.)

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colour. The brain was grossly normal, but was increased in weight to 1,365 g. The pituitary gland was normal.

On microscopic section, the heart showed hypertrophy and coronary atherosclerosis. The lungs showed metastatic calcification of the alveolar wall and peribronchial tissue. There was uraemic pneumonitis. The gastro-intestinal tract showed haemorrhage in the small intestine and multiple metastatic calcification of gastric glands. There was minimal fatty change in the liver. Metastatic calcification was present in the adrenal glands, but not in the spleen or pancreas. The pathologist's description of the kidney sections follows:

'Practically all glomeruli are fibrotic and there is very extensive atrophy of tubules. What glomeruli remain show at times adhesions and at times crescent formation. There is a marked interstitial fibrosis and inflammatory reaction with striking deposition of calcium throughout the renal parenchyma. Calcium is found in both cortex and medulla. At times it lies within tubular cells, at other times within glomeruli and most frequently appears to lie interstitially. There is extensive intimal proliferation of both small arteries and arterioles.' (See Fig. 10)

The bone marrow (Fig. 11) showed osteoporosis. Parathyroid tissue was hyperplastic.

## Discussion

Increased density of bone is seldom seen and always presents an interesting problem in diagnosis. The possibility of marble-bone disease was quickly dismissed when the serum calcium level was reported. It appeared highly likely that the excessive ingestion of vitamin D was the cause of his presenting complaints and striking findings. It is not possible to exclude hypervitaminosis A. Vitamins A and D are combined in most dose forms, and information regarding exact dose form is not available in the present instance.

That the excess deposit of mineral is actually a result of excessive vitamin ingestion seems likely in view of the following considerations. First, the history and findings apart from the skeleton are consistent with the known syndrome of vitamin D intoxication. Second, the dose and duration of ingestion of vitamin D were greatly excessive. Third, reported cases of vitamin D intoxication with bone demineralization were mostly older people and patients with rheumatoid arthritis. It is plausible to believe that skeletal maturity does not favour deposition of mineral salts. Furthermore, metabolic forces against skeletal mineralization exist in rheumatoid arthritis, an inflammatory disease with catabolic, or at least anti-anabolic effect on bone and other supporting structures.

It seems reasonable that a child's growing skeleton would react to a high concentration of circulating calcium by incorporating it in the skeleton at areas of epiphyseal and membranous growth. The distribution of excess mineral deposit in long bones is consistent with this type of orderly deposition. Known actions of vitamin D relate to improved absorption of calcium and phosphorus, rather than to specific effects at the level of bone mineralization. Thus it should be possible to correlate skeletal calcification with the level of serum calcium. A study of the ionized calcium level would have been valuable.

A striking parallel to the present case is seen in the cases reported as 'idiopathic hypercalcaemia' (Lowe, Henderson, Park and McGreal, 1954; Creery and Neill, 1954; Creery, 1953; Payne, 1952; Lightwood, 1952; Fellers and Schwartz, 1958; Fanconi, Girardet, Schlesinger, Butler and Black, 1952). The main clinical and laboratory features are similar, except for the onset and duration, and the presence of the 'elfin facies' and associated sequelae.

An interesting feature of the present case is the prompt reversal of bone density on discontinuance of vitamin D therapy. This began before evidence of renal failure appeared. Later progressive bone demineralization should properly be ascribed to renal failure with accompanying acidosis. A finding supporting this view is the presence at autopsy of osteoporosis in the bone sections, representing loss of more than the expected amount of bone substance. Closer observation of calcium metabolism might have changed the outcome. It is known that renal damage secondary to hypervitaminosis D is reversible. The presence of a constant steady stream of calcium from bone to blood stream was undoubtedly responsible for progressive unrelenting renal damage. It was not possible to test the effect of cortisone or other drugs on the serum calcium level.

The chief value of the present case report appears to be the demonstration of a mechanism for quantitative increase in bone mineral in humans. Many interesting studies could be planned on similar cases. It is hoped that the report of this case will stimulate others to make further careful observations in the rarely available similar situation.

## Summary

A case report of a young boy who ingested large quantities of vitamin D over a period of one year demonstrates that reversible increase in bone density may occur, with severe calcinosis and fatal renal failure.

The extent and distribution of the osteosclerosis differs from that reported in vitamin D overdosage in children and resembles somewhat the picture seen in the severe cases of 'idiopathic hypercalcaemia'.

I am indebted to R. S. Cleland, M.D., of the Children's Hospital of Los Angeles for permission to reproduce microscopic slides and to paraphrase and quote from the autopsy report. Credit is also due to Richard Schreiber, M.D., of the Orthopaedic Hospital, for aid in describing x-ray findings. George R. Woltmann, M.D., of the Children's Hospital staff was kind enough to provide data from his office files.

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# IDIOPATHIC HYPERCALCEMIA AND SECONDARY HYPERCALCEMIA INDUCED BY EXCESSIVE ADMINISTRATION OF VITAMIN D

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Flavio Vedovini
Italy

A syndrome characterized by idiopathic hypercalcemia associated with mental retardation, dwarfism, and osteosclerosis was first described by Fanconi in 1952. In that same year, Lightwood described a similar, but less grave, condition, characterized by arrested growth, anorexia, vomiting and constipation, with hypercalcemia and hyperazotemia. The form described by Fanconi has been given the name of grave form, while the second, more frequently encountered, is called the mild form of idiopathic hypercalcemia.

The symptoms of the form described by Fanconi are mental retardation, dwarfism, the characteristic facies with small cranium and protruding jaw, vomiting and constipation, muscular hypotonia, irritability, hypertension, polyuria and polydypsia, dehydration, loud parasternal systolic murmur, albuminuria, pyuria, increased elimination of calcium in the urine, hyperazotemia, hypercholesterolemia, hypercalcemia, alkaline phosphatase level sometimes increased but most often decreased, mild acidosis, osteosclerosis associated in some cases with premature closing of the sutures with craniostenosis. Also found on several occasions was facial paralysis in the peripheral area (Morgan et al., Kowarski). The malady is most often found in children under a year old. In Smith's case, the patient of 5 showed osteoporosis, transitory facial paralysis, and convulsive activity from numerous foci in the EEG (Smith et al.). Lang also observed manifestations of a xanthomatous type and hepatosplenomegaly, probably linked with hypercholesterolemia. Prognosis in the grave form is reserved, since it is tied in with the



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frequent apparition of irreversible renal insufficiency.

The symptoms in the mild form are more subtle. They include anorexia, vomiting, constipation, loss of weight, hyperazotemia, mild acidosis, hypercalcemia and hypercalciuria associated with a certain increase in bone density, and arterial hypertension (Wineberg, Lowe). The prognosis, if therapy is initiated early enough, is benign in such cases. However, the borderline between the grave and mild forms is not clearly defined.

Idiopathic hypercalcemia must be distinguished from secondary hypercalcemia following on primitive hyperparathyroidism, sarcoidosis, tumors, lukemia or Addison's disease, or from overdoses of vitamin D. The therapy is based on administration of cortisone to hinder intestinal absorption of calcium (Wineberg et al.), and sodium phytate, and on a diet of decalcified milk, either with Dent's method (Dent) or by the addition of 10% sodium sulphate (Kowarski). Sodium ethylene-di-amino-tetra-acetate used by some is not recommended by others because of a possible toxic reaction.

While cases of idiopathic hypercalcemia reported in the Anglo-Saxon and Swiss literature are numerous, and we know of two published reports in the French literature (Royer et al., Forfar et al.), there seems to have been no such case reported in the Italian literature.

We thought it might be helpful, therefore, to report two cases of mild idiopathic hypercalcemia handled in the Pediatric Clinic of the University of Siena, and to compare the various clinical and laboratory aspects of these with two cases of vitamin D poisoning we recently observed.

Case nº 1. - B. Angela, 9 months.

A.F. Nothing important to report.

A.P. Born normally at term. Birth-weight 3 kg. Was nourished on mother's milk for three months. At the end of that time, since the baby grew little, the maternal feedings were integrated with powdered skim-milk. At two months, a slight eczematous outbreak on the face, which spontaneously regressed about the third month. Bronchial pneumonia at 4 months. Starting then, the baby was given a vitamin compound containing 2000 U/cc of vitamin D1, in doses of 10 drops per day. Towards her fifth month, the baby began to exhibit irregular vomiting and anorexia. Weight gain since then has been extremely slight. Recently these symptoms have become accentuated. Vomiting has been more abundant and more frequent, and anorexia more pronounced. The baby shows abundant diuresis and intense thirst, with a tendency towards constipation.

Clinical examination. Subject hypotrophic, weighing 5.5 kg. Adipose layer scanty. Skin pale, slightly dehydrated. Visible mucosa pale. Muscular masses hypotrophic, hypotonic. Lymph glands unaffected.

Head: conformation regular. Antorior fontanello almost completely ossified. Eyes, ears, noso, mouth, pharynx all negative.

Thorax: Symmetrical, good expansion. Percussion and ascultation findings normal.

Heart: Murmurs within normal limits. Tones pure and clear at all foci. Pulse vigorous, fast.

Abdomen: pliant. Hypochondrial organs normal. Joints and articulation, negative. External genital organs normal.

Nervous system: No meningeal signs. Superficial and profound reactions normal. The baby is frotful, apathetic, shows little interest in her surroundings.

Laboratory examinations

G.R.: 3,900,000; G.B.: 8.700; Hb: 75%;VG: 97; N:44%; L:48%; E: 2%; M: 6%. Slight anisocytosis.

Urinalysis: S.V.: 1007; Cluc: abs; acotono: abs.; albumen: abs.; phenylpiuric acid: abs.; calciuria (Sulkowich)++++; sodiment: neg.

Antituberculin intradermoreaction: neg. Calcemia: 16mg%. Phosphoremia: 5.5 mg%. Alkaline phosphatase: 10.2 U.B. Glycemia: 106 mgr%. Alkaline reserve: 60 vol/liter. Azotemia: 30 mgr%. Phosphaturia: 37 mgr%. (185 mgr/24 hrs). Chloremia: 86 mEq/litor. Sedimentation rate: 22 mm/hr. Total protoins: 6.8 gr%. Electrophoresis: alb.: 60.3%;alpha1: 5%;alpha2: 11.2%;beta: 11.3% gamma: 8.8%. Eye socket examination: negative. Radiological examination of cranium: no signs of endocranial hypertension; no endocranial calcification. Radiological examination of the skeleton: no focussed skelotal altorations. Retarded appearance of ossification nuclei in the carpus. E.E.G.: normal. R.V. and comp.: negative. Radiological examination of the abdomen: no renal calcification. Radiological examination of the thorax: negative.

Course.

Following initiation of therapy, we observed a rapid normalization of the laboratory tests, paralleling the regression of clinical symptoms and a marked increase in weight.

At home, when prednisone therapy was arbitrarily discontinued, the baby remained well for some ten days, then began once again to exhibit marked anorexia, frotfulness, and vomiting. Returned to the clinic, she was found to have calcemia at 18mg%. Once again, the symptoms regressed rapidly following hydrocortisone therapy.

Two subsequent check-ups made one month and three months after her release, showed normal calcemia. Her condition is still good, and her bodily growth satisfactory. Data on this case are summed up in Table I.

Case nº 2. - M. Antonella, 6 months.
A. F. Nothing important to report.
A. P. Born normally at term. Birth-weight 4 kg.

Was nourished exclusively on mother's milk for 2 months. Then, due to agalactia in the mother, was given a formula of powdered skim milk. When admitted to the clinic, the baby had shown a slight fever for about a week (around 38ºC), marked anorexia, vomiting after almost every meal. The baby was also fretful and agitated, particularly at night. She had never been given any vitamin preparation.

Clinical examination

General condition rundown. Skin pale, not perfectly hydrated. Adipose layer scanty. Muscular masses hypotrofic, hypotonic. Lymph glands unaffected.

Head: Conformation regular. Anterior fontanelle normal to tense. Eyes, nose, mouth, ears, pharynx, negative.

Thorax: symmetrical, good expansion. Percussion and ascultation findings normal.

Heart: Murmurs within normal limits. Tones pure and clear at all foci.

Abdomen: Pliant. Hypochondrial organs normal.

Nervous system: The baby is fretful, but takes an interest in her surroundings and smiles at her mother. She can sit up alone. No meningeal signs. Superficial and profound reflexes normal.

Joints and articulation: no damage. External genital organs: normal in appearance.

Laboratory examinations:

Antituberculin intradermalreaction: negative. G.R.: 4,100,000; G.B.: 8,200; Hb: 80%; V.G.: 0.99; N: 45%; L: 50%; M: 4%; E: 1%. Urinalysis: S.W.: 1018; alb: abs.; glucose: abs.; acetone: abs.; calciuria (Sulkowich): ++; sediment: numerous exfoliation cells and 2-3 leucocytes in the field. Calcemia: 14.2 mg%. Glycemia: 88 mg%. R.W. and comps: negative. Azotemia: 44 mg%. Arterial pressure: max. 105, min 60. Phosphoremia: 3.5 mg%. Alkaline reserve: 68 vol / liter.

Radiological examination of thorax: negative.

Radiological examination of skeleton: no focussed osseous lesions. Slight hypercalcification in the femoral metaphyses.

Radiological examination of abdomen: no renal calcification.

Radiological examination of cranium: no signs of endocranial hypertension, no abnormal calcification.

Course (Table 2)

After a few days of hydrocortisone therapy (15 mg in di) and sodium diethylaminotetra-acetate (given intravenously in doses of 50 mg per kg in di for 5 days), the baby began to eat again. Fever and vomiting disappeared, general condition rapidly improved, and both blood and urine calcium levels dropped to normal. Blood nitrogen level quickly returned to normal. The baby was released after 20 days, completely recovered. About a month later, she was admitted again with an abcess on the left cheek. The symptoms described above had not returned, and she was gaining weight regularly. Blood analyses showed calcium levels still within normal limits (11.4 mg%), normal phosphorus, increased alkaline phosphatase (20 U.B.).

A check 4-½ months later in the out-patient clinic showed that the baby was in good general condition. Aside from a slight rise in the alkaline phosphatase level, laboratory findings were normal.

To sum up: here were two babies, aged 6 and 9 months, showing the same symptoms, basically vomiting, a halt in growth, and low fever, accompanied by hypercalcemia but without signs of renal involvement.

The first patient had received 800 units of vitamin D per day for several months, while the second had received only what vitamin D was in the powdered milk used for her formula.

Now we shall report briefly on the two cases of vitamin D intoxication we observed.

Case 1. - A. Roberto, 8 months.
A.F. - Nothing important to report.
A.P. - Born normally at term. Birth-weight 3.5 kg. Breast-fed exclusively for 7 months. From then on, breast-feedings were augmented with milk-and-coffee, hot cereal, biscuits and fruit-juice.

The baby had always been well, and grown normally until a month ago. At that time, a doctor prescribed a heavy dose of vitamin $D_2$, then a preparation very rich in vitamin $D_2$ (200,000 U/cc) in doses of 100,000 U per day. Since then, the baby has shown increasingly more marked anorexia, and irregular spurts of fever. Growth has stopped, and recently there has even been a weight loss. For several days, he has been paler than usual, extremely fretful, and has vomited repeatedly.

Clinical examination. Skin very pale, dehydrated. Mucosa quite moist. Subcutaneous adipose layer scanty. Lymph glands unaffected. Muscular masses hypotonic and hypotrophic. Skelotal system apparently unaffected.

Head: Conformation regular. Anterior fontanelle almost completely ossified. Eyes, ears, nose, mouth, pharynx negative. Hair very dry.

Thorax: Symmetrical; good expansion. Percussion and ascultation findings normal.

Heart: Murmurs within normal limits. Tones pure and clear from all foci. Pulse rhythmic, pounding. Arterial pressure: max. 140, min. 95.

Abdomen: Pliant. Hypochondrial organs normal.

Nervous system: The baby appears to have marked psychomotor agitation, accompanied by almost continuous crying. No neurological insufficiency or meningeal signs were noted. Profound and superficial reflexes normal.

Laboratory examinations

Antituberculin intradermoreaction: negative.

Urinalysis: Appearance: clear; color: pale yellow; Specific Weight: 1008; gluc.: abs.; albumin: slight clouding; acetone: abs.; calciuria (Sulkowich): ++++; Sediment: 10-20 leucocytes in the field, numerous exfoliation cells.

G.R.: 3,500,000; G.B.: 9,600; Hb: 75%; VG: 1; N: 56%; L: 40%; M: 3%; E: 1%.

Calcemia: 20 mg/%. Phosphoremia: 3.9 mg%; Phosphaturia: 38 mg% (120 mg/24 hrs). Alkaline phosphatase: 6.8 U.B.; Azotemia: 52 mg%; Alkaline reserve: 60 vol / liter;

Radiological examination of thorax: negative.

Radiological examination of skeleton: no osseous alterations, no modifications of normal growth processes.

Radiological examination of abdomen: no renal calcification.

Blood protoins: 8.20 gr%;

Electrophoresis: alb. 54.8%; alpha 1: 6.7%; alpha 2: 11.6%; beta: 12%; gamma: 14.4%. Blood sodium: 168.4 mEq/l. Blood potassium: 3.0 mEq/l. Total chlorine: 120 mEq/l. Urine pH: 6.30. Blood pH: 7.38. Blood cholesterin: 206 mgr%. Blood sugar: 98 mgr%.

Medullary biopsy: Scarcity of immature red-series elements. Numerous monocytoid elements. Normal maturation development of the white series.

E.C.G. Sinusoid rhythm. No signs of myocardial affection. Slight drop in the ST line on the precordial DD, probably indicating a slight hypopotassemia.
E.E.G. Normal.
Ophthalmoscopic examination: negative.

Course: (Table 3).

After 10 days of hospitalization, the baby's condition was slowly improving. Vomiting had disappeared, and the growth process resumed. The baby seemed calmer, and could sit up and play in bed. Blood calcium level returned to normal after about 10 days. Hyperazotemia also regressed, though somewhat slowly. Albuminuria and pyuria disappeared sooner. A month after admission, both blood pressure and azotemia were back to normal. After about two months, the baby was discharged in good general condition, and with the blood chemistry restored to normal.

Case 2. - F. Paolo, 6 months.

A.F. Nothing important to report.
A. P. Carried to term, normal birth (forceps used). Birth-weight 3 kg. Breast-fed for 15 days. Maternal agalactia caused switch to cow's milk. Growth was generally regular, though a bit slow. No vomiting. Stools always normal.

Starting some 20 days before admission, the baby had begun irregular vomiting, usually after feeding, and very copiously. Growth stopped. Constipation set in. Since then the patient has been very pale, fretful, agitated. The mother reports that since the baby was a month old she has been giving him 10 drops per day of a vitamin preparation very rich in vitamin D (200,000 U/cc).

Clinical examination. Weight 5.7 kg. Marked pallor of skin and mucosa. Subcutaneous adipose layer scanty. Muscular masses hypotonic. Lymph glands not affected.

Head: Conformation normal. Anterior fontanelle 2x2 cm. Normal to tense. Eyes, nose, mouth, pharynx: normal.

Heart: Murmurs within normal limits. Tones pure and clear at all foci. Pulse vigorous, rhythmic, normal frequency. Arterial pressure: max. 105, min. 60.

Thorax: Symmetrical, good expansion. Percussion and ascultation findings normal.

Abdomen: Pliant. Liver 2 cm from costal arc. Spleen within limits of normal.

Nervous system: The baby is fretful, but interested in his surroundings. No meningeal signs. Superficial and profound reflexes normal.

Joints and articulation normal.

External genitalia normal in conformation.

Laboratory examinations

Urinalysis: S.W. 1016. Albumen: none. Glucose: none. Acetone: none. Calcium (Sulkowich): ++. Sediment: a very few leucocytes. Phosphaturia: 39 mg% (114 mg/24 hours).

C.R.: 2,800,000. C.B.: 9.800. Hb: 54%. VG: 0.98. N: 28%. L: 66%. M: 6%.

Antituberculin intradermoreaction: negative. Calcemia: 16 mg%. Phosphoremia: 3.9 mg%. Alkaline phosphatase: 6.9 Bodanski units.

Radiological examination of thorax: negative.

R.A.: 62 vol/liter. Azotemia: 26 mg%. Natritemia: 136 mEQ/liter. Potassemia: 4 mEq/liter. Blood proteins: gr.6.5%. Electrophoresis: Albumen: 53.6%. Alpha $_1$: 7.4%. Alpha2: 11.8%. Beta: 13.7%. Gamma: 15.4%.

Radiological examination of skeleton: Normal bone development. Bone age parallels chronological age of patient. There is a slight density of the long bones in the spongey area, on the diaphysis of the growth cartilage.

Course (Table 4)

This patient's general condition improved rapidly. Six days after admission, the vomiting had ceased, and the baby had begun to eat again, and to make good weight gains. At the time of discharge, 20 days after admission, his blood calcium was altogether normal. (9 mg%).

One month after discharge, the baby was readmitted to the clinic for treatment of bronchitis. While at home he had not vomited, and had gained weight.

Blood chemistry tests produced normal results.

The symptoms, the laboratory findings, and the favorable outcome make it possible to make a firm diagnosis, for the first two patients, of idiopathic hypercalcemia. The diagnostic differential between these and the two babies with vitamin D poisoning was possible on the basis of case histories, since the clinical findings, like the laboratory test results, are practically identical. One of the patients with vitamin D intoxication, Roberto, exhibited a clinical picture of considerable gravity, with marked modifications in the blood nitrogen level associated with considerable arterial hypertension, anemia, obvious urinary

anomalies, and dehydration. These symptoms are quite similar to those of the grave forms of idiopathic hypercalcemia.

It is noteworthy that in Case 2, Antonella, the patient was brought to the clinic because she was running a low-grade fever. There was also a high fever at the time of admission of Roberto A, with grave symptoms of vitamin D intoxication. In that patient there was also an obvious state of psycho-motor agitation.

We do not have any exact knowledge of the pathogenesis of idiopathic hypercalcemia. Because of the possible change in the cholesterol metabolism, and because cases of renal calcification in myxedema patients, some have considered the possibility that such patients may be hypothyroid (Royer, Shiers, Illig). While this is not to be ruled out as a concomitant, it is probable that such forms are tied in with hypersensitivity to normal doses of vitamin D (Fanconi and Spahr), or to an alteration in the enzyme balance of the mechanism that regulates the absorption of this vitamin.(Stapleton & Evans). We already know that there are wide variations in individual sensitivity to this substance; and we know that doses strong enough to counteract rickets have produced, in such cases, high activity of the vitamin D type (Smith, Fellers). It is possible that such patients may have modifications in the sterol metabolism, with consequent increase of the endogenous precursors of vitamin D, which would be activated thereby (Fellers & Schwartz, Forfar). This hypothesis is apparently confirmed by the findings of high levels of vitamin A and of the lipoproteins (Fyfe, Forfar). The nature of these precursors is unknown. It is possible that one of them is a sterol different from vitamin D2: a cholesterol derivative, a substance of the estrogen type, or an abnormal adrenal hormone could be the unknown factor.

Corroboration for this hypothesis is found in the fact that the symptomatology of vitamin D intoxication, as shown in the cases we described as well, is practically identical with that of idiopathic hypercalcemia (Lefebre, Ross). The major alterations in both forms are to be found in the renal parenchyma, and they control the outcome of the disease. They are atrophy of the cortex and tubules and, in grave cases, diffuse renal calcification (Fanconi & Spahr, Fellers & Schwartz). Such alterations may be facilitated by other conditions. For example, it is known that a deficient and inadequate diet in rats clearly favors the deposit of calcium in the renal parenchyma, after induced experimental ergosterol poisoning(Chieffi). The excess of vitamin D causes a diminution of renal glomerular filtration and flux, and brings bout a lessened reabsorption of sodium by the tubular epitholium, with consequent hyposteneuria (Manitius). In a later stage, there is a deficiency in

tubular reabsorption of phosphates. These findings are presumably attendant upon the renal calcification that occurs in hypervitaminosis. In idiopathic hypercalcemia, however, it is possible that there is a primitive renal involvement (Girardet).

In conclusion: The cases we described prove that idiopathic hypercalcemia is a morbose syndrome that can also be seen in Italy. For this reason, it is advisable to the calcium levels in blood and urine of patients showing such symptoms as anorexia, vomiting, cessation of growth, and psycho-motor agitation. This disease should be distinguished from hypercalcemia linked with overdoses of vitamin D. In this case, the clinical symptoms are identical with those of idiopathic hypercalcemia. Hence the case-history data are the sole diagnostic element enabling one to distinguish one form from the other. The course of the disease can be favorable, as proved in the cases we report, in which we obtained clinical and general recovery, albeit with fluctuations in condition, through prolonged use of hydrocortisone and prednisone, associated in particularly grave cases with administration of sodium ethylenediaminotetraacetate.

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## SUMMARY

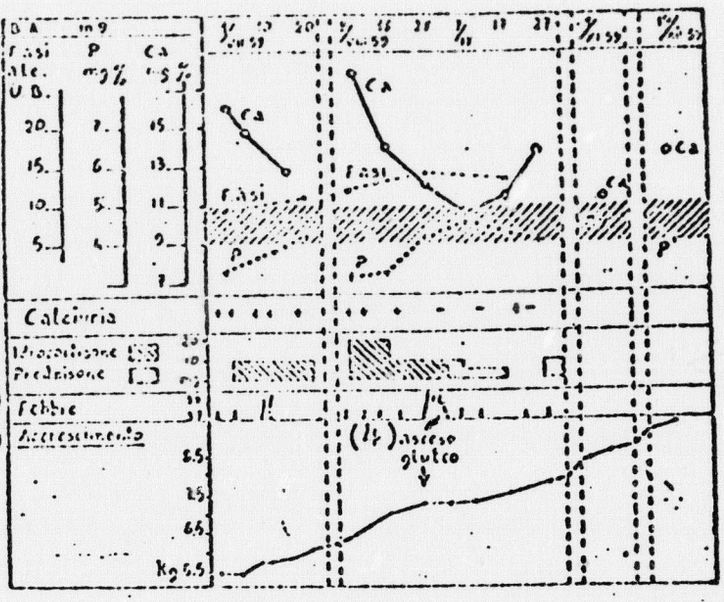
IDIOPATHIC HYPERCALCEMIA AND HYPERCALCEMIA SECONDARY TO OVERDOSE OF VITAMIN D. PRESENTATION OF FOUR CASES. - The writers present and compare two cases of idiopathic hypercalcemia with two cases of vitamin D intoxication.

In the first two patients, aged 6 and 9 months, the symptomatology included anorexia, vomiting, and growth failure. In one case there was a persistent low-grade fever. Both patients had received normal doses of vitamin D (about 800 U in di). Both cases showed hypercalcemia (16 mg% and 14.2mg%) and hypercalciuria (Solkowich +++). One patient displayed slight hyperazotemia. In both cases the course of the disease was quickly rendered favorable.

In the other two cases (8 and 6 months) the symptoms were anorexia, vomiting, growth failure, pallor, and listlessness. Both subjects had been given a preparation very rich in vitamin D (200,000 U/cc) over a considerable period, in doses of about 100,000 U in di. In the first case, laboratory reports showed marked hypercalcemia (20 mgr%), hypercalciuria, hyperazotemia, arterial hypertension, albuminuria and piuria. In the second, the findings were positive only for hypercalcemia (16 mgr%) and hypercalciuria. In both cases, therapy produced regression of the clinical symptoms and normalization of the blood chemistry.

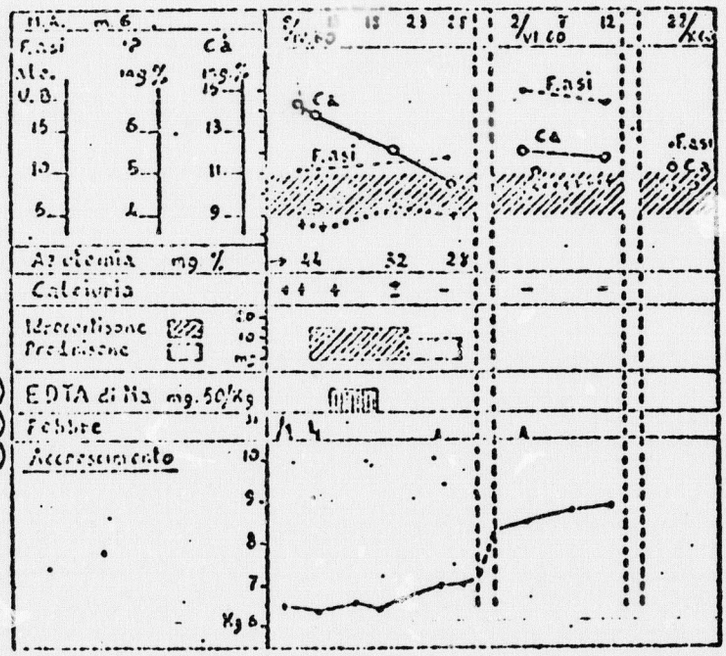
# TABLE APPENDIX

## Table 1



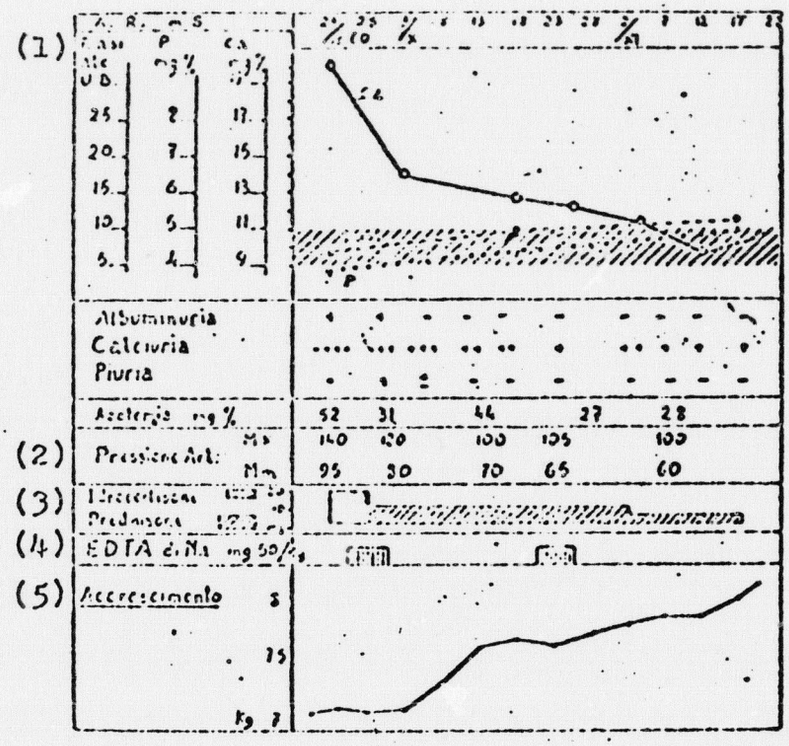

Key: 1) Alkaline phosphatase; 2) Fever; 3) Growth; 4) Gluteal increase

## Table 2



Key: 1) Alkaline phosphatase; 2) Sodium ethylene diamino tetra acetate; 3) Fever; 4) Growth. E515

Table 3




Key: 1) Alkaline phosphatase; 2) Arterial pressure; 3) Hydrocortisone-prednisone; 4) Sodium ethylene diamino tetra acetate; 5) Growth.

Table 4

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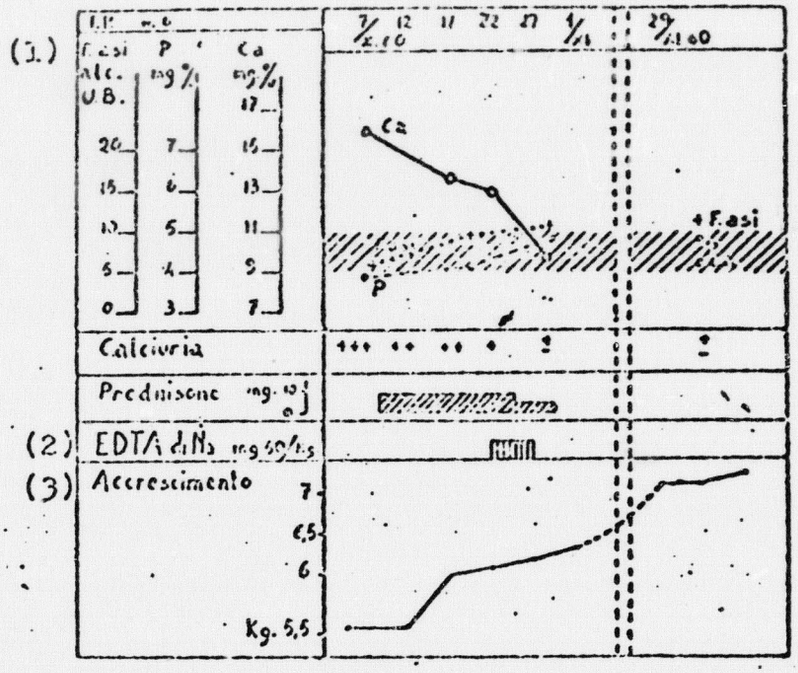


Key: 1) Alkaline phosphatase; 2) Sodium ethylene diamino tetra acetate; 3) Growth.

XXVIII.

Istituto di Clinica Pediatrica dell'Università di Siena
Direttore: Prof. A. Chiari

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irreversibili di insufficienza renale.

La sintomatologia della forma lieve è più sfumata. Essa è
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...ve. Il ritmo è ...
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...di ipercalcemia ed ipercalciuria, probabil-
...ipercalcemia idiopatica. La prognosi di detta forma gra-

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XXVIII.

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# Ipercalcemia idiopatica ed ipercalcemia secondaria ad eccessiva somministrazione di vitamina D

Dott. ALBERTO FOIS
*Libero Docente*

Dott. FLAVIO VEDOVINI
*Assistente straordinario*

Una sindrome caratterizzata da ipercalcemia idiopatica associata a ritardo mentale, nanismo ed osteosclerosi fu per primo descritta da FANCONI nel 1952. Nello stesso anno LIGHTWOOD descrisse una condizione simile ma di minore gravità, caratterizzata da arresto dell'accrescimento, anoressia, vomito e costipazione con ipercalcemia ed iperazotemia. Alla forma descritta da FANCONI è stato dato il nome di forma grave, mentre alla seconda, di più frequente osservazione, viene dato il nome di forma lieve di ipercalcemia idiopatica.

I sintomi della forma descritta da FANCONI sono rappresentati da ritardo mentale, nanismo, facies caratteristica con cranio piccolo e mascella sporgente, vomito e costipazione, ipotonia muscolare, irritabilità, ipertensione, poliuria e polidipsia, disidratazione, soffio sistolico parasternale rude, albuminuria, piuria, aumento dell'eliminazione del calcio urinario, iperazotemia, ipercolesterolemia, ipercalcemia, fosfatasi alcalina, più spesso diminuita, talvolta aumentata, acidosi lieve, osteosclerosi in qualche caso associata a saldatura precoce delle suture con cranio-stenosi. È stata inoltre notata talvolta paralisi periferica del facciale (MORGAN e coll., KOWARSKI). La malattia è stata generalmente osservata in bambini del primo anno di vita; nel caso di SMITH il paziente di 5 anni presentava osteoporosi, paralisi transitoria del facciale ed attività convulsiva a focolai multipli nello EEG (SMITH e coll.). Da LANG sono state anche osservate manifestazioni di tipo xantomatoso ed epatosplenomegalia, probabilmente legate alla ipercolesterolemia. La prognosi di detta forma gra-

ve è riservata, essendo legata alla frequente comparsa di fenomeni irreversibili di insufficienza renale.

La sintomatologia della forma lieve è più sfumata. Essa è rappresentata da anoressia, vomito, costipazione, perdita di peso, iperazotemia, acidosi lieve, ipercalcemia ed ipercalciuria associate ad un certo aumento di densità delle ossa, ipertensione arteriosa (WINEBERG, LOWE). La prognosi, se la terapia viene istituita tempestivamente, è in tali casi benigna. Non esiste peraltro un limite netto tra la forma grave e la forma lieve.

La ipercalcemia idiopatica deve essere differenziata da quella secondaria all'iperparatiroidismo primitivo, alla sarcoidosi, a tumori o a leucemie ed a malattia di Addison, oppure dovuta ad iperdosaggio di vitamina D. La terapia è basata sulla somministrazione di cortisone allo scopo di ostacolare l'assorbimento intestinale del calcio (WINEBERG e coll.), di fitato di sodio e su una alimentazione con latte decalcificato sia con il metodo di Dent (DENT) che mediante l'aggiunta di solfato di Na al 10% (KOWARSKI). L'etilendiamminotetraacetato di Na, impiegato da alcuni, viene sconsigliato da altri a causa di una possibile azione tossica.

Mentre relativamente numerosi sono i casi di ipercalcemia idiopatica riferiti nella letteratura anglo-sassone e svizzera, siamo a conoscenza di 2 pubblicazioni nella letteratura francese (ROYER e coll., FORFAR e coll.), mentre ci sembra che nessun caso di questo tipo sia stato riferito nella letteratura italiana.

Abbiamo ritenuto utile pertanto segnalare due casi di ipercalcemia idiopatica lieve ricoverati nella Clinica Pediatrica dell'Università di Siena, confrontandone i vari aspetti clinici e di laboratorio con due casi di intossicazione da vitamina D da noi recentemente osservati.

CASO N. 1. - *B. Angela*, m. 9.

*A. F.* Nulla di importante da rilevare.

*A. P.* Nata a termine da parto eutocico. Peso alla nascita Kg. 3.

È stata alimentata con latte materno per tre mesi. Dopo tale periodo, poichè la bambina cresceva poco, l'allattamento materno è stato integrato con latte in polvere mezza-crema. A 2 mesi modeste manifestazioni eczematose al volto, regredite spontaneamente verso il 3° mese. A 4 mesi bronco-polmonite. Da questo periodo è stato somministrato alla bambina un preparato polivitaminico contenente 2000 U/cc. di vit. D, alla dose di 10 gocce al giorno. Verso il 5° mese di vita la bambina ha cominciato a presentare vomito irregolare ed anoressia; l'accrescimento ponderale da allora è stato assai scarso. Negli ultimi tempi tale sintomatologia si è accentuata; il vomito si è fatto più abbondante e più frequente e l'anoressia più spiccata. La bambina presenta diuresi abbondante e sete intensa, l'alvo è tendenzialmente stitico.

E518

*E. O.* Soggetto ipotrofico, del peso di Kg. 5,500. Panniculo adiposo scarsamente rappresentato. Cute pallida, lievemente disidratata. Mucose visibili pallide. Masse muscolari ipotoniche, ipotoniche; linfoghiandole indenni.

*Torace*: di conformazione regolare. Fontanella anteriore quasi completamente ossificata. Nulla agli occhi, orecchi, naso, bocca, faringe.

*Torace*: simmetrico, ben espansibile. Reperto percussorio e ascoltatorio normale.

*Cuore*: nei limiti. Toni puri e netti su tutti i focolai. Polso valido, ritmico.

*Addome*: Trattabile. Organi ipocondriaci nei limiti. Nulla a carico degli arti e delle articolazioni. Organi genitali esterni normali.

*Sistema nervoso*: non segni meningei. Riflessi superficiali e profondi normali. La bambina è irrequieta, apatica, si interessa scarsamente allo ambiente.

*Esami di laboratorio.*

G. R.: 3.900.000; G. B.: 8.700; Hb: 75%; VG: 97; N: 44%; L: 48%, E: 2%; M: 6%. Lieve anisocitosi.

*Esame urine*: P. S.: 1007; Cloc.: ass.; acetone: ass.; alb.: ass.; acido benzoico: ass.; calciuria (Sulkowich): + + -; sedimento: negativo. *Intradermoreazione con tuberculina*: negativa. *Calcemia*: 16 mg.%. *Fosforemia*: 5,5 mg.%. *Fosfatasi alcalina*: 10,2 U. B. *Glicemia*: 105 mg.%. *Riserva alcalina*: 50 vol./litro. *Azotemia*: 30 mg.%. *Fosfaturia*: 37 mg.% (185 mg./24 ore). *Cloremia*: 86 mEq./litro. *Velocità di sedimentazione*: 22 mm./ora. *Proteine totali*: 6,8 g.%. *Tracciato elettroforetico*: alb.: 40,8%; $\alpha_1$: 5%; $\alpha_2$: 11,2%; $\beta$: 11,3%; $\gamma$: 8,8%. *Esame del fondo oculare*: negativo. *Esame radiologico del cranio*: non segni di ipertensione endocranica; non calcificazioni endocraniche. *Esame radiologico dello scheletro*: non alterazioni scheletriche a focolaio; ritardo della comparsa dei nuclei di ossificazione del carpo. *E. E. G.*: normale. *R. W. e compl.*: negative. *Esame radiologico dell'addome*: non calcificazioni renali. *Esame radiologico del torace*: negativo.

*Decorso.*

In seguito alla terapia instaurata si è osservato una rapida normalizzazione degli esami di laboratorio, parallelamente alla regressione dei sintomi clinici e ad un marcato aumento ponderale.

A domicilio, sospesa arbitrariamente la terapia con prednisolone, la bambina stette bene per circa 10 giorni, poi incominciò a presentare nuovamente inappetenza spiccata, irrequietezza, vomito. Ricoverata in Clinica per la seconda volta, fu riscontrata una calcemia di mg. 18%. La sintomatologia regredì rapidamente anche questa volta in seguito a terapia con idrocortisone.

Due controlli successivi, a distanza rispettivamente di circa un mese e 3 mesi dall'ultima dimissione, hanno messo in evidenza una calcemia normale. Le condizioni della bambina si sono mantenute buone e l'accrescimento ponderale soddisfacente.

I dati relativi a questo caso sono riassunti nella tabella N. 1.

Caso N. 2. - *M. Antonella*, m. 6.

*A. F.* Nulla di importante da rilevare.

*A. P. R.* Nata a termine da parto eutocico. Peso alla nascita Kg. 4. Allattamento materno esclusivo per 2 mesi. In seguito, per agalattia materna, alimentazione con latte in polvere mezza-crema.

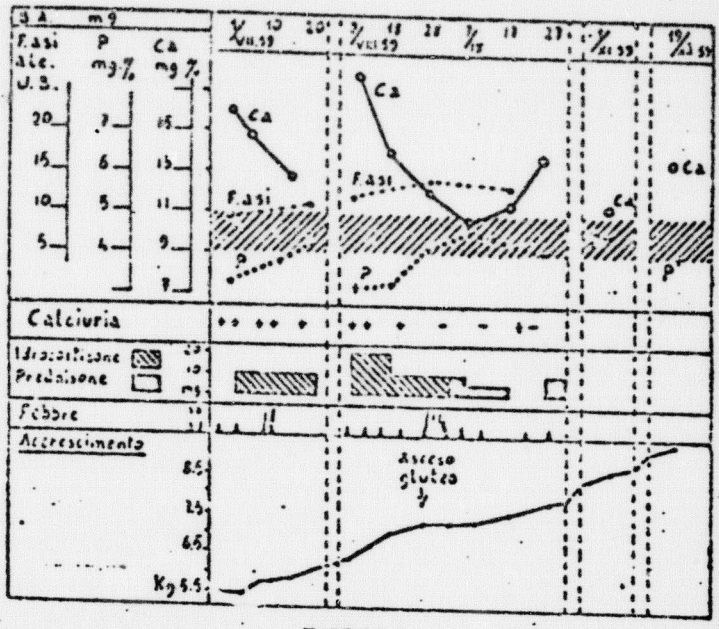


TABELLA I.

*A. P. P.* Da circa una settimana la bambina presenta qualche puntata febbrile sui 38°, anoressia spiccata, vomito quasi ad ogni pasto. La bambina è inoltre irrequieta, agitata, soprattutto di notte. Non sono mai stati somministrati preparati vitaminici.

*E. O.* Condizioni generali scadute. Cute pallida, non perfettamente idratata. Pannicolo adiposo scarsamente rappresentato. Masse muscolari ipotrofiche, ipotoniche. Linfoghiandole indenni.

*Testa*: di conformazione regolare. Fontanella anteriore normotesa. Nulla agli occhi, naso, bocca, orecchi, faringe.

*Torace*: simmetrico, ben espansibile. Reperto percussorio e ascoltatorio normale.

*Cuore*: aia nei limiti. Toni puri e netti su tutti i focolai.

*Addome*: trattabile. Organi ipocondriaci nei limiti.

*Sistema nervoso*: la bambina è irrequieta, ma si interessa all'ambiente e sorride alla madre. Si regge seduta. Non segni meningei. Riflessi superficiali e profondi normali.

*Arti ed articolazioni*: indenni. *Organi genitali esterni*: di aspetto normale.

*Esami di laboratorio.*

*Intradermoreazione con anatubercolina*: negativa. G. R.: 4.100.000; G. B.: 8.400; Hb.: 80 %; V. G.: 0,99; N: 45%; L: 50%; M: 4%; E: 1% *Esame urine*: P. S.: 1018; alb.: ass.; glucosio: ass.; acetone: ass.; calciuria (Sulkowich): + +; sedimento: numerose cellule di sfaldamento e 2-3 leucociti per campo. *Calcemia*: 14,2 mg.%. *Glicemia*: 88 mg.%. *R. W. e con-*

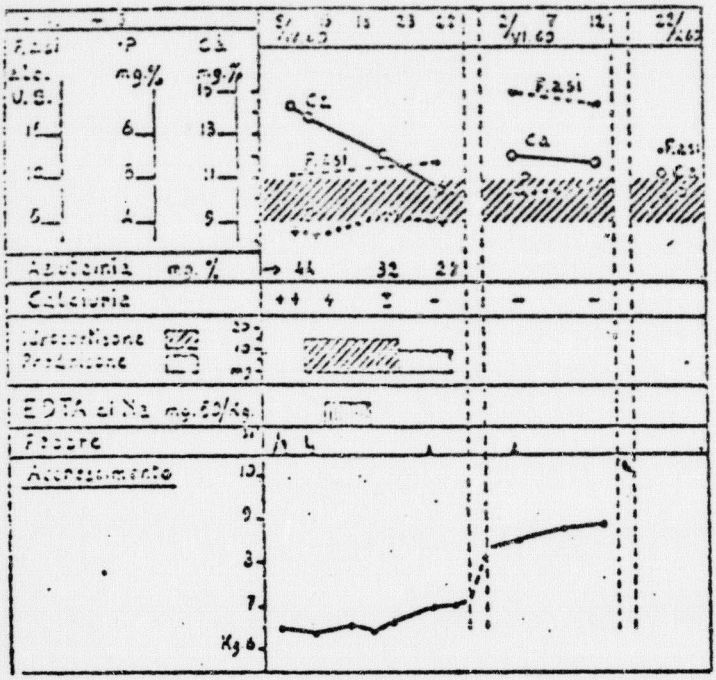


TABELLA 2.

*glicosuria*: negative. *Azotemia*: 44 mgr.%. *Pressione art.*: Mx 105, Mn 60. *Fosforemia*: 3,5 mgr.%. *Riserva alc.*: 68 vol./litro. *Esame radiologico del torace*: negativo.

*Esame radiologico dello scheletro*: non lesioni ossee a focolaio. Lieve ipercalcificazione nelle metafisi femorali.

*Esame radiologico dell'addome*: non calcificazioni renali.

*Esame radiologico del cranio*: non segni di ipertensione endocranica, né calcificazioni abnormi.

*Decorso* (Tab. N. 2).

Dopo pochi giorni di terapia con idrocortisone (15 mg. al dì) e dietilenodiamminotetracetato di sodio (somministrato per via endovenosa nelle dosi di mg. 50 pro Kg. al dì per 5 giorni) la bambina riprese ad alimentarsi, cessarono la febbre e il vomito, migliorarono rapidamente le condizioni generali e si normalizzarono sia la calcemia che la calciuria; l'azotemia ritornò rapidamente a valori normali. La bambina fu dimessa dopo 20 giorni di ricovero perfettamente ristabilita. Dopo circa un mese fu nuovamente ricoverata per un ascesso alla guancia sinistra. La sintomatologia precedentemente descritta non si era più ripresentata ed il peso corporeo era in regolare aumento. I reperti ematochimici misero in evidenza valori calcemici nei limiti della norma (11,4 mg%), fosforemia normale, fosfatasi alcalina aumentata (20 U.B.). In un controllo ambulatoriale effettuato a distanza di

4 mesi e mezzo dalla seconda dimissione, la bambina appariva in buone condizioni generali. Salvo un modesto aumento della fosfatasi alcalina gli altri reperti di laboratorio erano normali.

Riassumendo si tratta di due bambini rispettivamente di 6 e 9 mesi che hanno presentato una sintomatologia caratterizzata fondamentalmente da vomito, arresto dell'accrescimento e febbre modica, accompagnata da ipercalcemia senza segni di interessamento renale.

Nel primo paziente erano state somministrate da alcuni mesi 800 U. al giorno di vit. D, mentre nel secondo caso l'apporto di vitamina D era limitato a quello esistente nel latte in polvere impiegato.

Riferiamo ora brevemente i dati relativi ai due casi di intossicazione da vitamina D da noi osservati.

CASO N. 1. - *A. Roberto*, m. 8.

*A. F.* Nulla di importante da rilevare.

*A. P. R.* Nato a termine da parto eutocico. Peso alla nascita Kg. 3,500. Ha avuto allattamento materno esclusivo fino a 7 mesi. Da quest'epoca l'allattamento al seno è stato integrato con un caffè-latte, una farinata, qualche biscotto e succo di frutta.

*A. P. P.* Il bambino è sempre stato bene ed è cresciuto regolarmente fino ad un mese or sono. In tale epoca un medico ha prescritto una dose urto di vitamina D, e successivamente un preparato molto ricco di vitamina D, (200.000 U/cc.), nella dose di 100.000 U. al giorno. Da allora il bambino ha cominciato a presentare anoressia sempre più spiccata e puntate febbrili irregolari. L'accrescimento si è arrestato ed anzi negli ultimi tempi il peso è diminuito. Da qualche giorno il bambino è più pallido del solito, è estremamente irrequieto e presenta vomito ripetuto.

*E. O.* Cute molto pallida, disidratata. Mucose discretamente irrorate. Panniculo adiposo sottocutaneo scarsamente rappresentato. Linfoghiandole indenni. Masse muscolari ipotoniche e ipotrofiche. Sistema scheletrico apparentemente indenne.

*Testa*: di conformazione regolare. Fontanella anteriore quasi completamente ossificata. Nulla agli occhi, orecchi, naso, bocca, faringe. Capelli molto aridi.

*Torace*: simmetrico, ben espansibile. Reperto percussorio e ascoltatorio normali.

*Cuore*: aia nei limiti. Toni puri e netti su tutti i focolai. Polso ritmico, sceccante. Pressione arteriosa: Mx 140, Mn 95.

*Addome*: trattabile. Organi ipocondriaci nei limiti della norma.

*Sistema nervoso*: il bambino appare in preda ad una notevole agitazione psicomotoria, accompagnata da pianto quasi continuo. Non si notano deficit neurologici o segni meningei. Normali i riflessi profondi e superficiali.

*Esami di laboratorio.*

*Intradermoreazione con anatubercolina*: negativa.

*Esame urine*: aspetto: limpido; colore: giallo pallido; P. S.: 1008; gluc.: ass.; albumina: nubecola; acetone: ass.; calciuria (Sulkowich): + + + +; sedimento: 10-20 leucociti per campo e numerose cellule di sfaldamento.

G. R.: 3.500.000; G. B.: 9.600; Hb: 75%; VG: 1; N: 56%; L: 40%; M: 3%; E: 1%.

*Calcemia*: 20 mg.%. *Fosforemia*: 3,9 mg.%. *Fosfaturia*: 38 mg.%; (120 mg/24 h.). *Fosfatasi alc.*: 6,8 U. B. *Azotemia*: 52 mg.%. *Riserva alc.*: (0 vol./litro. *Esame radiologico del torace*: negativo. *Esame radiologico del-*

E520

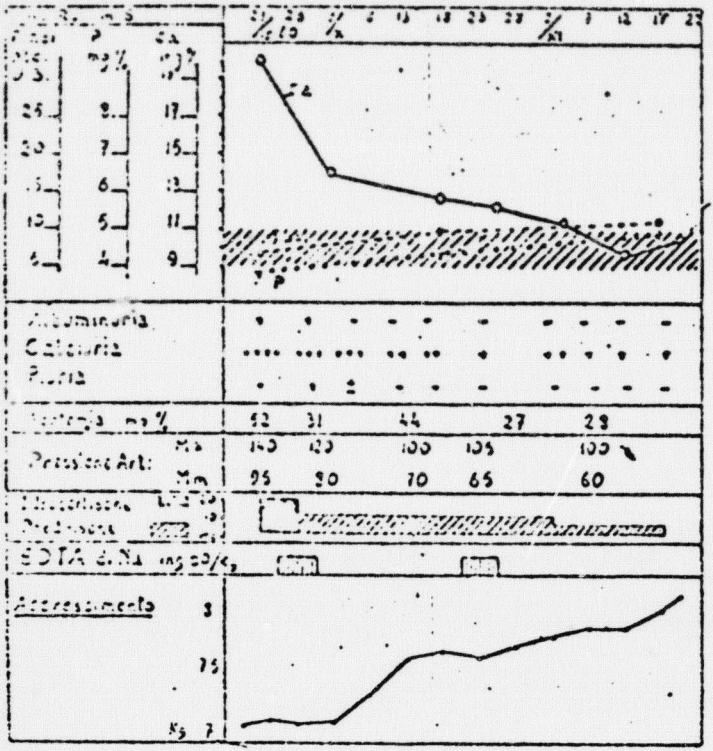

TABELLA 3.

*Ipo sthenia*: non si rilevano alterazioni ossee né modificazioni dei normali processi di accrescimento. *Esame radiologico dell'addome*: non calcificazioni renali. *Proteinemia*: 8,20 gr.%. *Tracciato elettroforetico*: alb. 54,8%; $\alpha_1$: 6,7%; $\alpha_2$: 11,6%; $\beta$: 12%; $\gamma$: 14,6%. *Natriemia*: 168,4 mEq/l. *Potassiemia*: 3,0 mEq/l. *Cloremia*: 120 mEq/l. *pH urine*: 6,30. *pH sangue*: 7,38. *Calcemia totale*: 10% mgr.%. *Glicemia*: 98 mgr.%.

*Esame midollare*: Gli elementi immaturi della serie rossa sono scarsamente rappresentati. Numerosi elementi di tipo megaloblastoide. Normale evoluzione maturativa della serie bianca.

*Esame E. C. G.*: ritmo sinusale. Non segni di sofferenza miocardica. Lieve peggioramento del tratto ST sulle DD. precordiali, probabile espressione di lieve ipopotassiemia.

*Esame E. E. G.*: normale.

*Es. Oftalmoscopico*: negativo.

**Decorso** (Tabella N. 3).

Dopo 10 giorni di ricovero, le condizioni del bambino andarono gradatamente migliorando con la scomparsa del vomito e la ripresa dell'accre-

scimento. Il bambino appariva più tranquillo e poteva star seduto sul letto e giocare. I valori della calcemia sono ritornati a livelli normali dopo circa 40 giorni. Anche l'iperazotemia è regredita con una certa lentezza, mentre più rapidamente sono scomparse l'albuminuria e la piuria. A distanza di un mese dal ricovero si erano normalizzate anche la pressione e l'azotemia. Il bambino è stato dimesso dopo circa 2 mesi in buone condizioni generali e con reperti ematochimici normalizzati.

Caso N. 2. - *F. Paolo*, m. 6.

*A. F.* Niente d'importante da segnalare.

*A. P. R.* Nato a termine di gravidanza da parto distocico (applicazione di forcipe). Peso alla nascita Kg. 3. Ha avuto allattamento materno per 15 giorni, poi per agalattia materna, è stato alimentato con latte vaccino. Lo accrescimento è stato sempre abbastanza regolare, anche se un po' stentato. Non ha mai presentato vomito; l'alvo è stato sempre regolare.

*A. P. P.* Da circa 20 giorni il bambino presenta vomito irregolare, in genere post-prandiale, a getto. L'accrescimento si è arrestato, l'alvo è divenuto stitico. Il paziente da allora è molto pallido, irrequieto, agitato. La madre riferisce che fin dal primo mese di vita ha somministrato al bimbo 10 gocce al giorno di un preparato molto ricco di vit. D (200.000 U/cc).

*E. O.* Peso Kg. 5.700. Pallore notevole della cute e delle mucose. Panicolo adiposo sottocutaneo scarsamente rappresentato. Masse muscolari ipotoniche. Linfoghiandole indenni.

*Testa*: di conformazione regolare. Fontanella anteriore cm. 2 × 2, normotesa. Nulla agli occhi, naso, bocca, faringe.

*Cuore*: aia cardiaca nei limiti. Toni puri e netti su tutti i focolai. Polso valido, ritmico, normofrequente. Pressione arteriosa: Mx 105, Mn 60.

*Torace*: simmetrico, ben espansibile. Normale reperto percussorio ed ascoltatorio.

*Addome*: trattabile. Fegato a 2 cm. dall'arco costale. Milza nei limiti.

*Sistema nervoso*: il bambino è irrequieto, ma si interessa all'ambiente. Non segni meningei. Normali i riflessi superficiali e profondi.

Atti ed articolazioni normali.

Organi genitali esterni di conformazione regolare.

*Esami di laboratorio.*

*Esame urine*: P. S.: 1016; albumina: ass.; glicosio: ass.; acetone: ass.; calciuria (Sulkowich): + + +; sedimento: qualche raro leucocita.

G. R.: 2.800.000; G. B.: 9.800; Hb: 54 %; VG: 0,98; N: 28 %; L: 66 %; M: 6 %.

*Intradermoreazione con anatubercolina*: negativa. *Calcemia*: 16 mg %. *Fosforemia*: 3,9 mg %. *Fosfatasi alcalina*: 6,9 U. Bodanski. *Esame radiologico del torace*: negativo. *R. A.*: 62 vol./litro. *Fosfatasia*: 39 mg % (114 mg/24 ore). *Azotemia*: 26 mg %. *Natriemia*: 136 mEq/litro. *Potassiemia*: 4 mEq/litro. *Proteinemia*: gr. 6,5 %. *Tracciato elettroforetico*: albumina 53,6 %; $\alpha_1$: 7,4 %; $\alpha_2$: 11,8 %; $\beta$: 13,6 %; $\gamma$: 13,4 %.

*Esame radiologico dello scheletro*: sviluppo osseo normale. L'età ossea concorda con l'età cronologica del paziente. A carico delle ossa lunghe si rivela un modesto addensamento a banda della spongiosa, sul versante diafisario della cartilagine di accrescimento.

*Decorso* (Tabella N. 4).

Le condizioni generali di questo paziente migliorarono rapidamente. Dopo 6 giorni dal ricovero scomparve completamente il vomito, ed il bam-

E521

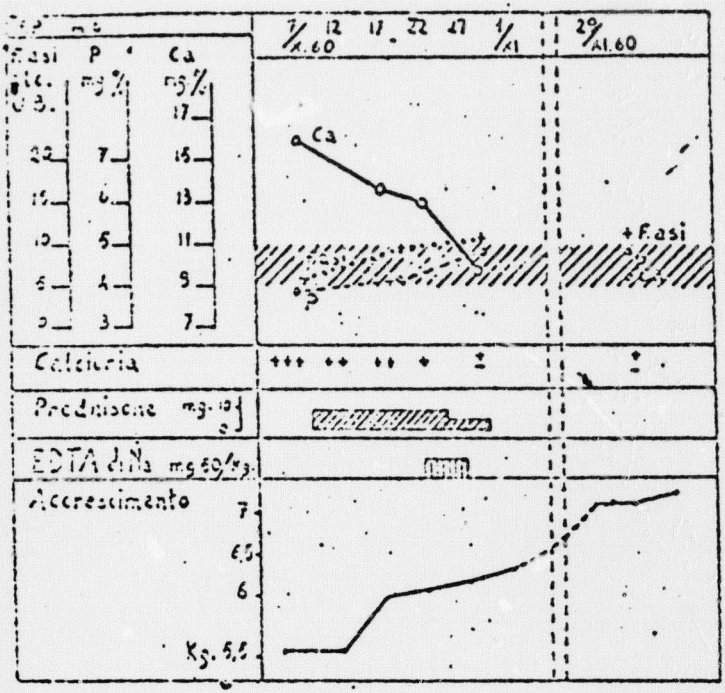


TABELLA 4.

bino riprese ad alimentarsi e a crescere bene in peso. Alla dimissione (dopo 20 giorni di degenza) la calcemia si era del tutto normalizzata (9 mg.%).

Il bambino ad un mese di distanza dalla dimissione è stato nuovamente ricoverato in Clinica per una bronchite. A domicilio non ha più presentato vomito ed è cresciuto in peso.

I reperti ematochimici sono risultati normali.

La sintomatologia, i reperti di laboratorio e l'esito favorevole consentono di porre nei primi due pazienti la diagnosi di ipercalcemia idiopatica. La diagnosi differenziale nei confronti dei due bambini con intossicazione da vitamina D. è stata possibile sulla base dei dati anamnestici, essendo la sintomatologia clinica ed i reperti di laboratorio praticamente sovrapponibili. Uno dei pazienti affetti da intossicazione da vitamina D (A.R.) ha presentato un quadro clinico di notevole gravità con marcate modificazioni della azotemia, associata a notevole ipertensione arteriosa, anemia, evidenti

alterazioni urinarie e disidratazione. Tale sintomatologia è ravvicinabile a quella delle forme gravi di ipercalcemia idiopatica.

È da notare che nel caso n. 2 (M.A.), il paziente è stato portato alla nostra osservazione per una febbricola. Temperatura febbrile elevata era pure presente al momento dell'ingresso del bambino A. Roberto con gravi sintomi di intossicazione da vit. D. In tale paziente esisteva inoltre un evidente stato di agitazione psico-motoria.

La patogenesi della ipercalcemia idiopatica non è esattamente conosciuta. A causa della possibile alterazione del metabolismo del colesterolo e poichè sono stati osservati casi di nefrocalcinosi in mixedematosi, si è pensato alla possibilità che esista in tali pazienti un certo grado di ipotiroidismo (Royer, Shiers, Illig). Pur non escludendo tale concausa è probabile che tale forma sia legata ad una sensibilità particolare a dosi normali di vitamina D (Fanconi e Spahr) o ad una alterazione enzimatica nel meccanismo che regola l'assorbimento di tale vitamina (Stapleton ed Evans). È noto infatti che esistono notevoli variazioni nella sensibilità individuale a questa sostanza e d'altro canto dosaggi del potere antirachitico del siero hanno dimostrato in tali casi una elevata attività di tipo vitaminico D (Smith, Fellers). È possibile che tali pazienti presentino modificazioni del metabolismo degli steroli con conseguente aumento di precursori endogeni della vitamina D che verrebbero da essa attivati (Fellers e Schwartz, Forfar). Tale ipotesi sarebbe avvalorata dal riscontro di livelli elevati di vitamina A e di lipoproteine (Fyfe, Forfar). La natura di tali precursori è sconosciuta. È possibile che si tratti di uno sterolo diverso dalla vitamina $D_3$: sia un derivato dal colesterolo che una sostanza di tipo estrogeno od un ormone surrenale abnorme, potrebbero rappresentare questo fattore sconosciuto.

Tale ipotesi è avvalorata dal fatto che la sintomatologia della intossicazione da Vit. D, come dimostrano anche i casi da noi descritti, è sovrapponibile a quella della ipercalcemia idiopatica (Lefebure, Ross). Le alterazioni più importanti in ambedue le forme di ipercalcemia si osservano a carico del parenchima renale e condizionano l'esito della malattia. Esse sono rappresentate da atrofia della corteccia e dei tubuli e, nei casi gravi, da una diffusa calcificazione dei reni (Fanconi e Spahr, Fellers e Schwartz). Tali alterazioni possono essere facilitate da altre condizioni. È noto ad esempio che una dieta carenzata ed insufficiente favorisce nettamente nel ratto, in cui si sia prodotta una intossicazione sperimentale con ergosterolo irradiato, la deposizione del calcio nel parenchima renale (Chieffi).

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L'eccesso di vitamina D provoca una diminuzione della filtrazione glomerulare e del flusso renale e determina un minor riassorbimento del sodio da parte dell'epitelio tubulare, con conseguente ipostenuria (MARRACK). In uno studio ulteriore diviene deficitario il riassorbimento tubulare dei fosfati. Questi reperti sono presumibilmente secondari alle calcificazioni renali che si verificano nella ipervitaminosi. Nella ipercalcemia idiopatica è possibile invece che esista un interessamento renale primitivo (GIRARDET).

*Concludendo*, i casi da noi descritti documentano che l'ipercalcemia idiopatica è una sindrome morbosa che può essere osservata anche in Italia. Per tale ragione è consigliabile controllare la calcemia e la calciuria in pazienti che presentino manifestazioni rappresentate da anoressia, vomito, arresto dell'accrescimento, agitazione psico-motoria. Tale forma morbosa deve essere differenziata dall'ipercalcemia legata ad iperdosaggio di vitamina D. In questo caso i sintomi clinici possono essere sovrapponibili a quelli dell'ipercalcemia idiopatica e pertanto è il dato anamnestico il solo elemento diagnostico capace a differenziare una forma dall'altra. Il decorso può essere favorevole come dimostrano i casi da noi riportati, nei quali si è ottenuta la guarigione clinica e umorale, sia pure attraverso varie vicende di miglioramenti e peggioramenti, con l'uso prolungato di cortisonici (idrocortisone e prednisone) associati, nei casi di particolare gravità, alla somministrazione di etilendiamminotetraacetato di sodio.

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RIASSUNTO. — Vengono presentati dagli AA. due casi di ipercalcemia idiopatica lieve e due legati ad iperdosaggio di Vitamina D.

Nei primi due pazienti, dell'età di 9 e 6 mesi rispettivamente, la sintomatologia era rappresentata da anoressia, vomito, arresto dell'accrescimento. In un caso era presente febbricola. Tali pazienti avevano ricevuto normali dosi di Vit. D (circa 500 U. al giorno). In entrambi i casi era presente ipercalcemia (mg. 16 e 14,2% rispettivamente) e ipercalciuria (Sulkowich: + + +). Nella seconda bambina esisteva anche un modesto aumento dell'azotemia. Il decorso fu rapidamente favorevole.

Negli altri due casi, dell'età di 8 e 6 mesi rispettivamente, la sintomatologia era costituita da anoressia, vomito, arresto dell'accrescimento, pallore, agitazione psico-motoria. In entrambi i soggetti era stato somministrato per lungo tempo un preparato molto ricco di vitamina D (200.000 U. per cc.) alla dose di circa 100.000 U. al giorno. Nel primo caso i reperti di laboratorio dimostrarono, notevole ipercalcemia (20 mg.%), ipercalciuria, iperazotemia, ipertensione arteriosa, albuminuria e piuria. Nel secondo caso erano presenti solamente ipercalcemia (16 mg.%) ed ipercalciuria. La terapia adottata determinò la regressione della sintomatologia clinica e la normalizzazione dei reperti emato-chimici.

HYPERCALCÉMIE IDIOPATIQUE ET HYPERCALCÉMIE SECONDAIRE À L'INTOXICATION DE VITAMINE D. PRÉSENTATION DE 4 CAS. — Les AA. rapportent deux cas d'hypercalcémie idiopathique légère et deux en rapport à l'intoxication de vitamine D. Chez les deux premiers sujets âgés respectivement de 6 et de 9 mois la sintomatologie était représentée par anorexie, vomissement, arrêt de croissance, et, dans un cas, température fébrile. Ces sujets avaient reçu des doses normales de vitamine D (presque 500 U par jour). Chez les deux cas on observait une hypercalcémie (mg 16 et 14,2 respectivement) et hypercalciurie (Sulkowitch + + +). Chez la deuxième fillette il y avait aussi une modeste élevation de l'azotémie. L'évolution a été rapidement favorable.

Chez les deux autres sujets, âgés respectivement de 8 et de 6 mois auquels on avait administré pour une longue période une préparation riche en vitamine D (200.000 U. par cc) avec une posologie de 100.000 U. par jour, la sintomatologie était representée par anorexie, vomissement, arrêt de croissance, agitation psychomotrice. Chez le premier sujet les recherches de laboratoire ont démontré une forte hypercalcémie (20 mg%), hypercalciurie, hyperazotémie, hypertension arterielle, albuminurie et piurie. Chez le deuxième sujet on observait seulement hypercalcémie (16 mg%) et hypercalciurie. Le traitement employé a déterminé la regression de la sintomatologie clinique et la normalisation des données endochimiques.

IDIOPATHIC HYPERCALCAEMIA AND HYPERCALCAEMIA SECONDARY TO HYPERABSORPTION OF VITAMIN D. PRESENTATION OF 4 CASES. — The AA. present two cases of idiopathic hypercalcaemia together with two cases of vitamin D intoxication.

In the first two patients, aged 9 and 6 months respectively, the symptomatology was represented by anorexia, vomiting and growth failure. In one case a long standing

low grade fever was present. These patients had received normal doses of vitamin D (about 500 U. per die). In both cases hypercalcemia (mgr. 16 and 14,2% respectively) and hypercalciuria (Sulkowich + + +) were present. In one patient a slight hyperazotemia was noted. The course of the illness was rapidly favourable.

In the other two cases (age 8 and 6 months respectively) the symptomatology was characterized by anorexia, vomiting, growth failure, polyuria, and listlessness. Both subjects had received for a long time a preparation very rich in vitamin D (200.000 per cc with a dosage of about 1000000 pro die). In the first case the laboratory reports proved a remarkable hypercalcemia (20 mgr. %), hypercalciuria, hyperazotemia, arterial hypertension, albuminuria and pluria. In the second case only hypercalcemia (16 mgr. %) and hypercalciuria were present. The therapy brought up the regression of the clinical symptomatology and the normalisation of the blood chemistry.

IDIOPATHISCHER UND SEKUNDÄRER HYPERCALZEMIE BEI ÜBERDOSIERUNG VON D-VITAMIN. — Die VV. beschreiben 2 Fälle leichter idiopathischer Hypercalzemie und weitere 2 Fälle, die auf Überdosierung von D-Vitamin zurückzuführen sind.

In den ersten beiden Patienten, 9 und 6 Monate alt, waren die Symptome durch Anorexie, Erbrechen, Stillstand des Wachstums vertreten. In einem Fall war leichtes Fieber vorhanden. Die Patienten hatten normale D-Vitamindosen (ungefähr 500 U. am Tag erhalten. In beiden Patienten traten Hypercalzemie (16 mgr-prd 14,2%) und Hypercalciurie (Sulkowich + + +) auf. In dem zweiten Mädchen war auch eine leichte Erhöhung der Azotämie vorhanden. Der Verlauf war sehr schnell günstig beobachtet.

In den anderen beiden Fällen, 8 und 6 Monate alt, waren die Symptome Anorexie, Erbrechen, Wachstumsstillstand, Blässe, psychisch-motorische Erregung. In beiden Patienten war für lange Zeit ein sehr D-Vitamin-reiches Präparat (200.000 pro cc zu Dosen von je 1000000 pro Tag verabreicht worden. Im ersten Fall zeigten die Laboratoriumsbefunde ein bemerkenswertes Auftreten von Hypercalzemie 20 mgr %), Hypercalciurie, Hyperazotemie, arteriellen Hypertension, Albuminämie und Pluria. Im zweiten Fall traten nur Hypercalzemie (16 mgr %) und Hypercalciurie auf. Die angewandte Therapie bestimmte den Rückgang der Klinischen Symptomatologie und die Normalisierung der humoralchemischen Befunde.

HIPERCALCEMIA IDIOPÁTICA E HIPERCALCEMIA CONSIGUIENTE DE HIPERDOSIFICACIÓN DE VITAMINA D. PRESENTACIÓN DE CUATRO CASOS. — Presentan los AA. dos casos de hipercalcemia idiopática leve y dos casos consiguientes de hiperdosificación vitamina D.

En los dos primeros casos, el uno de nueve y el otro de seis meses de edad, la sintomatología estaba representada por anorexia, vómito, arresto de crecer. En un caso se manifestó también estado febril. Han sido suministradas normales dosis de vitamina D (cerca 500 U. cada día). En los dos casos se observan hipercalcemia, (respectivamente mgr. 16% y 14,2%) e hipercalciuria (Sulkowich + + +). En el segundo caso se evidencia también un cierto acrecentamiento de azotemia. El curso de la enfermedad puede resultó favorable.

En los otros dos casos, el uno de ocho y el otro de seis meses de edad, la sintomatología consistía en anorexia, vómito, arresto de crecer, pallidez, inquietud psicomotriz. En los dos casos se suministró por largo rato un preparado muy rico en vitamina D (200.000 cada cc) en dosis de casi 1000.000 cada día. En el primer caso, los hallazgos de laboratorio manifestaron notable hipercalcemia (20 mgr. %), hipercalciuria, hiperazotemia, hipertensión arterial, albuminuria y emisión de orina poliúrica. En el segundo caso se manifestaron tan sólo hipercalcemia (16 mgr. %) e hipercalciuria. La terapéutica adoptada determinó la regresión de la sintomatología clínica y la normalización de los hallazgos humorálmicos.

XXIX.

ISTITUTO DI CLINICA PEDIATRICA DELL'UNIVERSITÀ DI PISA
Direttore: Prof. A. CANTILE

# Ipodisproteinemia acuta idiopatica nel bambino (*)

Dott. GIAMPAOLO GELLI Dott. LUCIANO DELLA SANTA

Le condizioni di disproteinemia apparentemente primitive sono di osservazione tutt'altro che frequente e, mentre molti dei loro problemi etiopatogenetici permangono oscuri, la delimitazione nosologica delle diverse forme è invece sufficientemente stabilita.

Da un punto di vista clinico infatti sembra che possano essere distinte alcune forme tra le quali le più importanti sono le agammaglobulinemie e le ipoproteinemie idiopatiche, da altri denominate « essenziali », da altri ancora « primitive ».

Nelle « agammaglobulinemie pure » non si rilevano modificazioni apprezzabili della proteinemia totale nè delle percentuali delle altre frazioni proteiche, mentre con le indagini elettroforetiche si evidenzia nel tracciato assenza completa delle gamma-globuline, svelabili in minima quantità solo per mezzo di indagini immuno-chimiche. Conseguenza di questa alterazione del quadro proteico ematico, che nel bambino viene riferita ad un difetto congenito (BRUTON; JANEWAY; HAYLES e KULNEFF) è una spiccatissima diminuzione delle difese immunitarie che conduce all'insorgenza frequente di infezioni di notevole gravità (BRUTON; BRUTON e Coll.; MCKHORY; KEIDAN e Coll.; JANEWAY; JEAN; MARTIN; DELAITRE e FONTY; HAYLES e Coll.; HARRIS e SCHICK; BERNHEIM e Coll.; ARNAUD-BATTANDIER; LEVESQUE; RITOSSA).

Nella « ipoproteinemia idiopatica » invece (pur verificandosi qualche volta l'insorgenza di fatti infettivi particolarmente gravi), il

(*) Il lavoro spetta in parti uguali agli Autori.

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# Metabolic studies in a patient with idiopathic hypercalcemia of infancy

*An asymptomatic 3½-month-old female infant who was receiving 1,000 units of supplemental vitamin D per day and whose serum calcium concentration was 14.5 mg. per cent was studied. While ingesting a diet containing less than 50 I.U. of vitamin D per day, the serum calcium fell to normal and the vitamin D concentration in the serum was normal. Subsequent ingestion of 400 I.U. of vitamin D for a 10 day period induced hypercalcemia, probable elevation of the serum vitamin D concentration and hypercalcuria. Sixteen days after discontinuing the vitamin D the serum calcium concentration was normal. There appeared to be a direct correlation between the amount of vitamin D ingested and the serum calcium and vitamin D concentrations. Severe idiopathic hypercalcemia had previously been noted in a sibling who had an elevated vitamin D concentration. The familial incidence of idiopathic hypercalcemia of infancy has rarely been recognized. There are no previous reports in which hypercalcemia and rise in plasma vitamin D were produced by a physiologic dose of vitamin D during the inactive phase. It is suggested that idiopathic hypercalcemia may, in some cases, be an inborn error of metabolism with defective inactivation of vitamin D, and that asymptomatic siblings of known cases of idiopathic hypercalcemia should be investigated for the mild form of the disease.*

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H. E. Harrison, M.D., H. C. Harrison, Ph.D., and R. M. Blizzard, M.D.

PITTSBURGH, PA.

THREE unusual aspects of a case of idiopathic hypercalcemia of infancy are being documented. First, the patient had asymptomatic and transient hypercalcemia although an older sister previously had severe idiopathic hypercalcemia.[1] A familial incidence of idiopathic hypercalcemia has only rarely been recognized. Second, this is the first recorded case of idiopathic hypercalcemia of infancy in which elevation of the serum calcium and probable elevation of the serum vitamin D level have been produced during the recovery phase by administering a physiologic dose of 400 units of vitamin D per day.

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*Dr. Kenny and Dr. Aceto were supported by Trainee Grant No. 2A-5219, United States Public Health Service.*

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## CASE REPORT

K. H., born Oct. 26, 1960, was admitted to the Harriet Lane Home on Feb. 14, 1961, at 3½ months of age for investigation of asymptomatic hypercalcemia.

The family history was significant because an older sister, S. H., aged 11½ years, was treated for hypercalcemia at 5 years of age.[1] She continues to have mental retardation, impaired renal function, azotemia, and seizures even though the serum calcium values have been normal since 1956. An older brother, 14 years of age, had an unremarkable history. The mother, father, brother, and sister are normocalcemic at this time.

Inquiry regarding the prenatal history revealed that Mrs. H. took 1 Natilet tablet per day from the third month of gestation until the time of delivery. Each tablet contained 250 mg. of calcium and 400 units of vitamin D. She drank only 1 glass of homogenized milk (400 units D per quart) per week, ate 1 or 2 eggs per day (25 to 70 units of vitamin D per egg), and ate no fish.

The infant weighed 4 pounds, 12 ounces when born at 38 weeks' gestation. Except for firm or hard bowel movements from the time of birth, the history was unremarkable, and the baby was described as being happy. This was in contrast to her older sister, who was an abnormally irritable child from birth until the hypercalcemia was eventually corrected.

A formula of evaporated milk, diluted with an equal volume of water, was given from birth until the age of 3 months. This contained 400 U.S.P. units of vitamin $D_3$ per quart. By the age of 3 months the infant was taking almost a quart each day. She also received 0.6 c.c. of Tri-vi-sol per day, which contained 1,000 units of calciferol.* From the age of 3 months until the time of admission at 3½ months, she received whole milk containing less than 50 units of vitamin D per quart.[2]

On Jan. 28, 1961, at the age of 3 months, K. was seen by us only because the older sister had had idiopathic hypercalcemia. Although the baby was clinically normal, the serum calcium determined in the hospital laboratory was 11.5 mg. per cent. Three days later the serum calcium was performed in our laboratory and was 13.5 mg. per cent. All subsequent calcium determinations were performed in our laboratory, unless otherwise specified. On February 8 the value was 12.6 mg. per cent, and on February 10, 12.7 mg. per cent. She was then admitted to the hospital for further study.

At the time of admission the blood pressure was 75/50 mm. Hg and the pulse was 100 per minute. The height was 23.5 inches, and the weight was 10 pounds, 1 ounce. The general appearance was not "elfin" and the physical examination was perfectly normal. There was no cardiac murmur. The hemoglobin was 12.1 Gm. per 100 ml. and the hematocrit 36 per cent. The white blood count was 10,800 per cubic millimeter. The urine was clear; the specific gravity was 1.014; the pH, 5.5; and the tests for protein, sugar, and diacetic acid were negative. The Sulkowitch test was 3-plus. By microscopic examination, 5 to 10 white blood cells per high-power field were seen. The urinary specific gravity was 1.020 after a 9 hour thirst.

The radiologists found that the ends of the long bones and the base of the skull were suggestively increased in density, but this was not definite.

After a 9 hour thirst the serum urea nitrogen was 35 mg. per cent; carbon dioxide-combining power, 14.9 mM per liter; sodium, 147 mEq. per liter; chloride, 101 mEq. per liter; potassium, 5.1 mEq. per liter; and the cholesterol, 270 mg. per cent. One week later without a preceding thirst, a serum urea nitrogen was 24 mg. per cent and a $CO_2$-combining power was 21.6 mM per liter.

## METHODS

Vitamin D activity in the serum was assayed by one of us (M. P.) who utilized the method of Bills.[3] The levels of serum calcium were determined by the method of Harrison and Harrison,[4] serum phosphorus by Fiske and Subbarow's method,[5] and serum citrate by the method of Natelson, Pincus, and Lugovoy.[6] Dr. Mackenzie Walser measured the serum magnesium[7] and Dr. Harold Nitowsky determined the serum vitamin E levels by the method of Quaife, Scrimshaw, and Lowry.[8]

Urinary calcium was determined by the method of Clark and Collip.[9] Stool calcium

*In January, 1961, the manufacturer changed the dosage of vitamin D in Tri-vi-sol from 1,000 to 800 units per 0.6 c.c. The baby did not receive the new product until vitamin D was administered during the studies which are described later.



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During the period when the calcium balance data were accumulated, Alacta of the same stock number, which contained less than 40 units of vitamin D per 100 Gm. of dry powder, was used as the only source of food. Analysis of this revealed a calcium content of 1,110 mg. per 100 Gm. of dry powder. Between February 14 and March 11, 105 Gm. per day was given and between March 12 and April 3, 125 Gm. per day. The intake was accurately determined by weighing each formula bottle before and after the feeding. Complete 24 hour urine and 72 hour stool specimens, the latter marked by carmine red, were collected while the patient was on a metabolic bed designed specifically for infants.

## RESULTS OF EXPERIMENTAL STUDIES

See Fig. 1 on which are charted serum vitamin D levels, serum, urine, and stool calcium concentrations, and calcium balance on the regimens described below.

**Hypercalcemia, plus recovery phases.** Since the normal mean serum calcium value in our laboratory is 10.1 mg. per cent with a standard deviation of ± 0.7 mg. per cent, 5 elevated values for serum calcium were recorded before the value of 10.4 mg. per cent* was obtained 21 days after discontinuing the vitamin D supplement and vitamin D-enriched milk. At this time the serum magnesium was 3.3 mg. per cent, which is within normal adult limits. Subsequent calcium determinations varied between 11.0 and 11.9 mg. per cent until 400 international units (I.U.) of vitamin D were added to the diet. The serum vitamin D level on February 16 was 2 I.U. per milliliter of serum, and less than 1 unit on February 21. Three determinations of serum citrate were also normal; these were 2.3, 1.7, and 2.8 mg. per cent between February 2 and February 24. A fourth value for serum citrate obtained on serum drawn February 17 was elevated to 4.0 mg. per cent. On February 26 and February 28 the serum vitamin E levels were normal (0.31 mg. per cent and 0.44 mg. per cent). A vitamin E absorption test was also normal. The vitamin E concentration was 2.66 mg. per cent 9 hours after a dose of 20 mg. per kilogram of tocopherol and the vitamin E absorption index was 13.0 units.

Study with vitamin D. 400 units of vitamin D per day were given from March 3 through March 12. Prior to starting vitamin D, the serum calcium was 11.0 mg. per cent. On the third day of vitamin D administration, it was 11.1 mg. per cent, and on the seventh day, 11.5 mg. per cent. Seventy-two hours after the last dose, the calcium was 12.9 mg. per cent, and 90 hours after that dose, 12.4 mg. per cent. One week after discontinuing vitamin D, the serum calcium was 12.4 mg. per cent. All three of these values are more than 3 standard deviations above the normal mean of serum calcium as determined in our laboratory. Sixteen days later the value had decreased to normal levels.

Serum vitamin D levels increased concomitantly with the serum calcium. The concentration of vitamin D was 3 units per milliliter on the day prior to vitamin D administration; on the third day, the level was 4 units or more; on the thirteenth day, 90 hours after the last dose of vitamin D, the level was probably 8 units or more. Unfortunately only 2 rats were used for this assay which precludes a dogmatic statement regarding the concentration. It should be noted that the initial serum vitamin D level was normal, at a time when the patient's serum calcium was decreasing to normal levels. Had this test been performed earlier in the course of the disease, it is possible that an elevated level would have been found.

Hypercalciuria was observed during and just after the 10 day course of vitamin D. The average urinary calcium excretion was 47 mg. per day during the precontrol period. During vitamin D administration, the average urinary value was 87 mg. per day. In the

*This value was determined in Dr. Mackenzie Walser's laboratory at the same time as the magnesium determination.

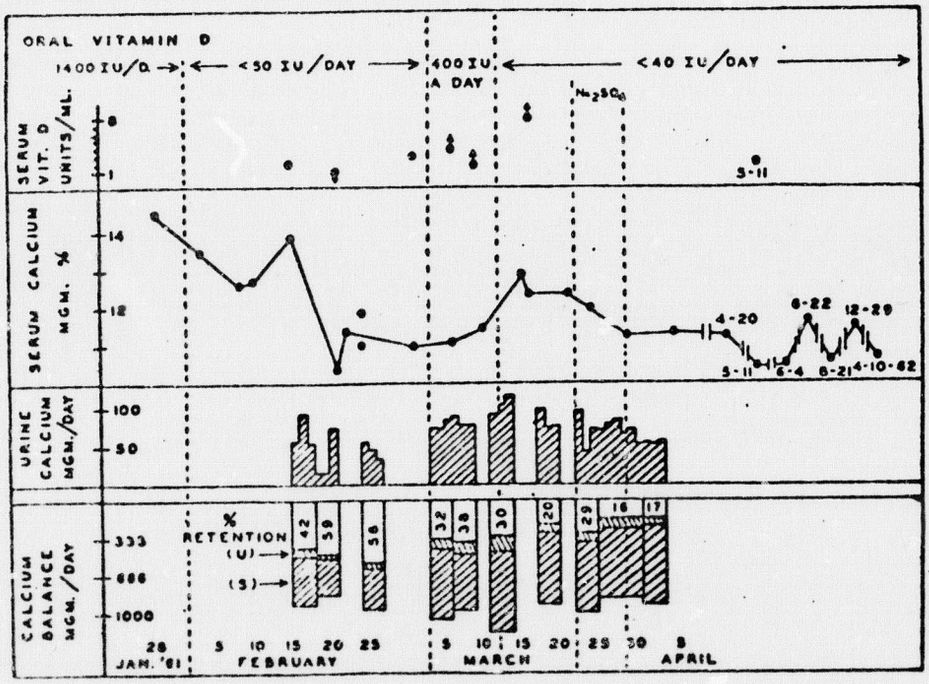


Fig. 1. Serum vitamin D levels, serum, urine, and stool calcium concentrations, and calcium balance on regimens described in text.

period from 24 to 48 hours after the last day of vitamin D administration, a peak excretion of 118 mg. of calcium was obtained.

There was no elevation of serum citrate 90 hours after discontinuing the vitamin D.

Study with sodium sulfate without added vitamin D. On March 22, 10 per cent sodium sulfate was begun in a dosage of 25 c.c. per liter of formula. This was given for 6⅔ days. The average intake of sulfate on this regimen was 7 mEq. per kilogram per day. Prior to starting the sulfate, the serum calcium was 12.1 mg. per cent; on the third day of sulfate administration the value was 12.0 mg. per cent, and on the day when sulfate was discontinued, 11.3 mg. per cent. This was 16 days after the last dose of vitamin D and may merely represent a slow fall in serum calcium, such as that observed the first time vitamin D was discontinued.

Low vitamin D diet. A low vitamin D diet, without fish or eggs and with nonirradiated milk, was then begun and has been continued to the present. Subsequent serum calcium determinations were 11.4 mg. per cent on April 4, 11.3 mg. per cent on April 20, 10.5 mg. per cent on May 11, and 10.4 mg. on June 5.

At the age of 1 year the height and weight were 28.5 inches and 15.8 pounds. The serum calcium was 11 mg. per cent. Six months later the height was 30 inches and the weight 20.3 pounds, and the mental development was normal. The serum calcium was 10.7 mg. per cent.

Balance data. An attempt was made to obtain calcium balance data. Reliance cannot be placed on precise quantitative interpretation of balance data because of errors inherent in the technique.[14] However, the *relative* changes in calcium balance reflect changes in regimen.

During the first time that the serum calcium was falling to normal levels, urine and fecal calcium were measured. During 3 successive 72 hour periods, 42.5, 59, and 56 per cent of the calcium ingested were retained. The average retention was 476 mg. per day. During the ten day period when 400 units per day of vitamin D were

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administered the calcium retention was 32, 38, and 30 per cent for 3 successive 72 hour periods, or an average retention per day of 331 mg. Forty milligrams of this reduced retention of calcium were attributable to an increased urinary loss. After vitamin D administration and before starting sodium sulfate, 19.6 per cent of ingested calcium was retained for the one 72 hour period measured. The mean retention was 172 mg. of calcium per day.

No definite effect of sodium sulfate administration was demonstrated. During the period of 6⅔ days when the patient received sodium sulfate, the effect of vitamin D was waning. In the initial three day period on sulfate, the per cent of calcium retained was 29.5 per cent and the actual value was 295 mg. per day. Although this represents an increased calcium retention when compared to the control period immediately preceding, the period is too short for one to state unequivocally that calcium retention was augmented by sodium sulfate. Sulfate was given for the first 3⅔ of the next 6 days, and during this six day period the percentage retained was 16 per cent; the actual amount was 130 mg. per day. During the subsequent three day control there was essentially no change as 17.5 per cent or 156 mg. of calcium were retained per day.

## DISCUSSION

One of the unusual aspects of this case is the familial incidence. This occurrence may indicate that some cases of idiopathic hypercalcemia result from an inborn error of metabolism.

In the literature there are only a few reports of idiopathic hypercalcemia occurring in more than one member of a family. Illig and Prader[10] reported idiopathic hypercalcemia in binovular twins whose sister had an elevated serum calcium. Forfar[11] has seen 2 and probably 3 sets of affected siblings among 11 families in which he has observed idiopathic hypercalcemia. Since K. H. had such a mild form of idiopathic hypercalcemia that it could have been overlooked, we would suggest that this entity may occur more frequently in siblings than has been documented.

Although abnormal metabolism of vitamin D has been suspected as causing this disease, Fellers and Schwartz[12] and Smith, Blizzard, and Harrison[1] who reported S. H., K. H.'s older sister, are the only authors who have recorded elevated serum levels of vitamin D during the active phase. Warkany and Mabon[13] noted the normal value for children to be 0.66 to 1.65 I.U. of vitamin D per milliliter of plasma. Fellers and Schwartz[12] found levels between 1.72 and 1.95 I.U. per liter of serum when studying normal infants. In the present case, the rise in the serum calcium to 12.9 mg. per cent and the probable rise in serum level of vitamin D to 8 units or more per milliliter, shortly after giving a test supplement of 400 units per day for 10 days, suggests that this disease sometimes is caused by defective inactivation or removal of vitamin D.

Short-term calcium balance studies on small infants are subject to error and the results are not precisely quantitative. Fomon[14] stresses the usefulness of balance technique in obtaining relative results, i.e., as a comparison of two regimens of management in a single subject. He cautions, "The successful use of metabolic balance studies [in obtaining comparative data] has suggested to some individuals that results are precisely quantitative. . . . Were this true . . . the change in nitrogen or calcium content of the body could be calculated." He discusses the reasons why "such calculations fail to provide valid estimates." With this caution in mind, and realizing that any losses in collection of excreta will falsely elevate apparent retention, the following observations are made. K. H. retained much calcium early during the recovery phase. Similar retentions are recorded during the active phase of idiopathic hypercalcemia by several authors who studied babies of comparable size. Morgan and his co-authors[2] reported 517 mg. per day retention in a 5.5 kilogram baby; Stapleton, McDonald, and Lightwood[15] found 500 mg. per day retained by an 8-month-old infant; Forfar and his associates[16]

recorded retentions of 445, 470, and 429 mg. per day in 3 infants with the active phase of idiopathic hypercalcemia.

The slight fall in calcium retention when 400 units of vitamin D was given daily was unexpected. This response was in contrast to those observed by Forfar[16] who gave 100,000 units of vitamin D per day to 3 patients. When administered to a patient during the active phase, this dosage increased the retention from 48 to 73 per cent; when given to a patient in the early recovery phase, the calcium retention rose from 16 to 40 per cent; and when given to a patient in the inactive phase, the retention increased from 16 to 42 per cent. A possible explanation for the unexpected results in our patient may be that the intestine was maximally absorbing calcium prior to the administration of the vitamin D, but the test dose still may have acted upon the bone with mobilization of calcium. The resulting increased urinary excretion of calcium then could partially account for the decreased positive calcium balance. This hypercalcuria (118 mg. per day) which occurred with the test dose of vitamin D was not unexpected since hypercalcuria has been reported consistently during the acute phase of the disease.[1, 16] The hypercalcuria probably resulted from the increased concentration of calcium in the blood and glomerular filtrate because of the action of vitamin D on bone. However, a direct effect of vitamin D on the renal tubules cannot be excluded. It is of interest that Forfar[16] did not consistently produce hypercalcuria when he administered vitamin D during the recovery phase.

The balance study with sodium sulfate was undertaken since oral administration of this salt was found by Kowarsky[17] to lower the serum calcium in an infant with idiopathic hypercalcemia. In his patient the serum calcium returned to normal levels within a 7 day period after administration was begun. No balance data was obtained during his study. In the present study, oral administration of sodium sulfate produced no significant change in the urinary excretion of calcium or in the calcium balance.

During the entire period while balance data was collected, there was a steady decrease in calcium retention. This steady decrease appears to have been relatively unaffected by the test dose of vitamin D or by sulfate administration, except for the increase in urine output of calcium during and immediately after the vitamin D test period. This increase associated with the rise in serum calcium is indicative of a response to vitamin D with respect to mobilization of calcium from bone, even though intestinal absorption of calcium remained unaltered.

During the inactive phase of the disease, the retention of 130 to 150 mg. per day of K. H. is comparable with retention of calcium by normal infants, discussed by Jeans and co-workers,[18] Daniels and Stearns,[19] Swanson,[20] and Harrison.[21]

Idiopathic hypercalcemia occurs in both a mild and a severe form. Forfar, Tompsett, and Forshall[22] have suggested that the severe type of the disease ensues when the diagnosis and treatment of the mild form are delayed. In support of this contention Daeschner and Daeschner[23] noted that the interval between the onset and the diagnosis in the severe form averaged 13 months, while the interval was 6 months in 52 mild cases. After evaluating the renal histology from routine autopsies of children, Shanks and MacDonald[24] suggested that idiopathic hypercalcemia of the mild form occurs much more frequently than it is diagnosed. It is impossible to know whether K. H. would have developed severe hypercalcemia if she had continued to receive normal or excessive amounts of vitamin D, or whether the hypercalcemia would have been transient. Yet the occurrence of both a mild and a severe form of the disease in the same family supports the thesis that both forms are manifestations of the same disease, but differ only in their severity.

## SUMMARY

A 3½-month-old infant, the sister of a patient previously reported with severe idiopathic hypercalcemia, was presented with asymptomatic and transient hypercalcemia in

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infancy has been described. Physical examination revealed a normal baby without "elfin" appearance. The serum calcium and urea nitrogen were elevated, but the serum phosphorus, alkaline phosphatase, and serum citrate were normal. The serum vitamin D concentration was 3 I.U. or less during the recovery phase, but became elevated to 8 units or more when 400 units of vitamin D per day was given for 10 days. At this time hypercalcemia and hypercalcuria occurred, although there was no increase in calcium retention during the period of vitamin D administration. At a time when the serum calcium was still elevated, administration of sodium sulfate had no appreciable effect on the serum calcium or the calcium balance.

It is suggested that "idiopathic hypercalcemia" may, in some cases, be an inborn error of metabolism with defective inactivation of vitamin D, and also that the disease may be found more commonly among asymptomatic siblings of known cases than has previously been reported.

We express our gratitude to Dr. John Peck, who permitted us to study this child; to Manuel DeGuzman for technical assistance; and to Mrs. Mary Westervelt for secretarial assistance.

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## Vitamin D activity of plasma in idiopathic hypercalcaemia

By W. F. J. CUTHBERTSON, *Glaxo Research Ltd, Greenford, Middlesex*

Idiopathic hypercalcaemia is a condition noted in young children, from a few months to a few years old, and is so called because of the absence of any obvious cause for the typical elevated levels of serum calcium. The signs and symptoms of the disease have been described by Lightwood (1952*a*,*b*), Payne (1952), Fanconi, Girardet, Schlesinger, Butler & Black (1952), Lightwood & Stapleton (1953) and Creery (1953). The condition is characterized by hypercalcuria, hypercalcaemia, acetonuria and renal dysfunction. There is also an increased absorption of Ca from the intestine, elevation of serum citrate level, increased renal phosphate reabsorption and growth retardation; all these effects are closely similar to those noted after administration of excess vitamin D (Fellers, 1959), except that in idiopathic hypercalcaemia there is usually no evidence that abnormally large amounts of vitamin D have been administered.

Lightwood & Stapleton (1953) observed that the disease could occur in one or other of two forms, the benign or mild, and the severe. The signs listed above are noticeable in both types of patient, but those with the severe form typically display several further features, physical and mental retardation, osteosclerosis and cardiac systolic murmurs, and they frequently demonstrate a typical facies known as 'elfin' face; the severe condition may be chronic and so further developed than the benign or mild form, which may be a more acute and transient manifestation of the disease.

The toxic manifestations, the renal and cardiac damage, the osteosclerosis and the mental and physical retardation are probably the result of the elevated serum Ca levels, because the disease can be controlled by measures that control serum Ca, e.g. cortisone administration, induction of a negative Ca balance by administration of a diet low in Ca or low in Ca and rich in phytic acid, or administration of ethylenediaminetetra-acetate (EDTA) (Creery & Neill, 1954; Ferguson & McGowan, 1954; Denham-Carter, Dent, Fowler & Harper, 1955; Stapleton, McDonald & Lightwood, 1956; Morgan, Mitchell, Stowers & Thomson, 1956).

Investigators have frequently remarked on the close correspondence between the condition noted in vitamin D intoxication and idiopathic hypercalcaemia (e.g. Lone, Mackenzie, Park & McGreal, 1954; Creery, 1953; Creery & Neill, 1954; Schlesinger, Butler & Black, 1956; Lightwood & Stapleton, 1953; Denham-Carter *et al.* 1955; Fellers, 1959; Morgan *et al.* 1956; Fellers & Schwartz, 1958*a*; Rhaney & Mitchell, 1956) and it has indeed been suggested that this condition may be in fact vitamin D intoxication in children especially susceptible to the toxic action of this vitamin (Morgan *et al.* 1956).

The observation that idiopathic hypercalcaemia is much rarer in the USA, Canada and Sweden than in the UK has also been put forward as evidence that vitamin D may be implicated (Morgan *et al.* 1956), because, in 1956, the vitamin D

content of infant milk foods was lower in those countries (about 40 i.u./100 ml in the USA) than in the UK (about 130 i.u./100 ml). Since 1957 the vitamin D content of infant dried milks in the UK has been reduced (now about 40 i.u./100 ml), and the vitamin D content of infant cereal foods has also been similarly decreased (from about 600–1000 i.u./oz to about 200 i.u./oz) thus markedly decreasing the average vitamin D intake of children in this country. It is not yet possible to state whether these changes have been associated with a significant reduction in the incidence of idiopathic hypercalcaemia, which, over the past few years, has amounted to about seventy to eighty cases yearly.

Idiopathic hypercalcaemia could easily be explained if there had been an excessive intake of vitamin D (and no evidence for it could be discovered in most instances in spite of detailed inquiries). An abnormal sensitivity to the vitamin, an abnormally high absorption and retention, a decrease in breakdown of the vitamin or its elimination from the body or an abnormality in Ca metabolism might also each offer an explanation for this disease.

Vitamin D activity can normally be demonstrated in a number of tissues of the body, since these tissues, or suitable extracts thereof, when orally administered to rachitic rats may cure rickets to some degree. Only in a very few instances has the compound responsible for this vitamin D activity been identified, by, for instance, radiochemical methods combined with chromatographic and chemical procedures (Kodicek, 1950; Kodicek & Ashby, 1960; Kodicek, Cruickshank & Ashby, 1960). Thomas, Morgan, Connor, Haddock, Ellis & Howard (1959) have shown that the vitamin D activity of serum is non-dialysable, that this activity is located, after electrophoresis, between the $\alpha_1$- and $\alpha_2$-globulins and that it is so whether the vitamin D (ergocalciferol) is administered to the patient before examination of the serum or added to the serum sample in vitro. Assay of pooled human serum fractions demonstrated vitamin D activity in the α-globulin-containing fractions (IV-1, IV-4), with traces in fraction IV but none in fractions I, II or III. Fellers (1959) reported that the vitamin D activity of the serum of a child receiving 60 000 i.u./day was distributed about equally between the α-lipoprotein and albumin fraction and the high-density β-lipoprotein fraction. From these observations it may be concluded that the vitamin D activity of serum is probably due to the presence of a compound having vitamin D activity and associated with a macromolecule.

Little is known of the fate of vitamin D when administered in physiological doses because of the extreme difficulty of measuring the minute quantities involved. Cruickshank & Kodicek (1953), Kodicek (1956) and Fellers (1959) followed the fate of ergocalciferol by radiochemical procedures, using $^{14}$C-marked ergocalciferol, or by biological methods after administering large doses (40 000 i.u.) to the rat. These workers have shown that, under these conditions, the concentrations in the liver 24 h after dosing were much higher than in the blood and other tissues, but that, within the next few days, the concentrations fell more rapidly in the liver than in the blood. Cruickshank & Kodicek (1953) also showed that only a small proportion of the administered vitamin D could be recovered from the test rats (6% after 1 day and less than 2% after 4 days). This poor recovery was shown, by tests with $^{14}$C-

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marked ergocalciferol (Kodicek, 1956; Kodicek & Ashby, 1960) to be due partly to poor absorption and partly to degradation of the vitamin within the body. The percentage absorption and degradation were also found to be similar for doses of 40 000 i.u. or 400 i.u./rat, and, at least at 24 h after administration, the vitamin concentrations were higher in the liver than in the other organs of rats given either of these doses. Vollmer (1939) demonstrated vitamin D activity (about 20 i.u./g) in skin and liver samples obtained at post-mortem from a child who had been given, within the 3½ days before death, 1·6 × 10⁶ i.u. vitamin D.

Eaton, Spielman, Loosli, Thomas, Norten & Turk (1947) showed that liver concentrations in the young calf were initially higher than plasma concentrations of the vitamin after administration of 30 000 i.u. vitamin D, but that the plasma concentration fell only slowly during the subsequent 42-day period. Heymann (1937) noted in the rabbit that 1 week after administration of 200 000 United States Pharmacopeia units of vitamin D the vitamin activity was higher in blood plasma than in the other tissues and that plasma levels remained higher than those in other tissues for at least the next 12 weeks. In a series of tests on dogs and rabbits, Warkany (1936, 1937) showed, like Heymann (1937), that the serum vitamin D activity, once elevated by administration of a single large dose (100 000 United States Pharmacopeia units of vitamin D), only slowly returned to previous levels (4–6 weeks), even though the initial rise in vitamin D activity was rapid, occurring within the first 1 or 2 days after dosing.

[There is little evidence as to the relative concentrations of the vitamin in liver and blood under physiological conditions, but Devaney & Munsell (1935) reported the vitamin D activity of liver from pigs, sheep and cattle as ranging from about 0·1 to 0·5 i.u./g, and Warkany (1937) has shown the vitamin D activity of serum samples from these species to be between about 0·5 and 1·5 i.u./ml. Thus, under physiological conditions the liver reserves may be small compared with the quantity circulating in the blood.]

In the pig, Quarterman, Dalgarno & Adam (1963) have shown that, after treatment for 1 month with daily doses of 250 000 i.u. vitamin $D_3$/day, the vitamin D activities of the liver and blood were both elevated to about the same extent (to 27 and 23 i.u./g respectively), whereas at a much lower dose level (350 i.u./day) the liver had an activity only about half that of the blood (0·21 and 0·52 i.u./g respectively). Within a week of withdrawal of the vitamin $D_3$ doses, it was noted that the vitamin D activity of the liver in both groups had fallen to about half that of the blood. Blood vitamin D activities steadily fell over the next 6 months, to 0·15 and 0·08 i.u./g in those groups that had been given the high and low doses of vitamin respectively. Liver vitamin activities were found to be about half those of the blood in both groups throughout this period.

Most of the blood vitamin D activity has been shown to be in the plasma rather than the corpuscles (Hess, Light, Frey & Gross, 1932). The foregoing observations would suggest that, at least when large doses of the vitamin, whether vitamin $D_2$ or vitamin $D_3$, are administered, some of it may be preferentially deposited in the liver, though within a relatively short period the liver concentration may fall as

that in the blood may then be higher. At lower, presumably physiological, doses, the blood levels are higher than those of the liver and all other organs examined.

In man the vitamin D activity of blood serum was found, in Cincinnati, to be about 1 i.u./ml (Warkany, 1936; Warkany & Mahon, 1940), whereas in Baltimore (Thomas *et al.* 1959) and in the UK (Cuthbertson, 1963) a similar but slightly higher mean value (about 2 i.u./ml serum or plasma) was reported. The liver vitamin D activity has been determined in two subjects (Cuthbertson, 1963), both aged 10–12 months. The control, not suffering from any disease of Ca metabolism, showed an activity of about 3 i.u./g liver, but the hypercalcaemic patient's liver contained less, about 1 i.u./g liver. Serum vitamin D assays were not carried out on either subject, but it can be seen that the liver activity was not greatly different from what would have been expected in the plasma of these patients.

The serum vitamin D activity may quickly be raised in man by administering the vitamin; with daily doses the rise may continue from a few hours after the first dose to reach a maximum level after several weeks (Thomas *et al.* 1959; Warkany, Geest & Grabill, 1942). As in animals, the serum activity, once elevated, is slow to subside, several months at least being required for return to normal levels (Warkany *et al.* 1942).

Table 1. *Serum vitamin D activity (i.u./ml) of patients given daily doses of ergocalciferol for periods of more than 1 month*

| Daily dose (i.u.) | Serum vitamin D activity: Arthritic patients (Warkany *et al.* 1942) | Hypoparathyroid patients (Thomas *et al.* 1959) |
|---|---|---|
| 50 000 | 16·5 | 40, 40 |
| 100 000 | — | 30, 48, 50 |
| 150 000 | 66 | — |
| 180 000 | 33 | — |
| 200 000 | 44 | 18, 8 |
| 240 000 | 33 | — |
| 400 000 | 130, 90 | — |
| 500 000 | 90, 130 | — |

Table 1 shows the maximum serum vitamin D activities attained in two groups of patients who had been prescribed known high levels of the vitamin for periods of time never less than 1 month and mostly considerably longer. One group (Warkany *et al.* 1942) suffered from chronic proliferative arthritis and the other (Thomas *et al.* 1959) from hypoparathyroidism. The results in Table 1 clearly show that the serum vitamin D activity cannot be precisely predicted from the dose given. Even the level attained with a constant dosage may vary unpredictably (Warkany *et al.* 1942), but in at least one patient, and perhaps in others, part of this variation may have been due to failure to take the dose prescribed. Thomas *et al.* (1959) have shown that the relation between serum Ca level and serum vitamin D activity is also variable. Thus it appears that there are from one person to another large quantitative differences in response to a given dose of vitamin D.

A number of determinations of vitamin D activity have been made on se
(or plasma) samples from patients with idiopathic hypercalcaemia and are summ
ized in Table 2 (Lang & Eiardt, 1957; Fellers & Schwartz, 1958*a*,*b*; Fellers, 19
Thomas *et al.* 1959; Smith, Blizzard & Harrison, 1959; Cuthbertson, 1963).

Table 2. *Vitamin D activity of plasma from patients with idiopathic hypercalca*

| Reference and country of origin of samples | No. of patients and type* of idiopathic hypercalcaemia | Serum (or plasma) vitamin D activity (i.u./ml) | Time taken for vitamin D activity to decline to normal level (months) |
|---|---|---|---|
| Lang & Eiardt (1957); W. Germany | 1, severe | 4 | ~8 |
| Fellers & Schwartz (1958*a*); USA | | 20–30 | >18 |
| Fellers & Schwartz (1958*b*); USA | 3, severe | 40–60 | >17 <26 |
| Fellers (1959); USA | | 20 | ? |
| Thomas *et al.*† (1959); UK | 2, mild | Normal (1–3) | — |
| Smith *et al.* (1959); USA | 1, severe | 23 | >6 |
| Cuthbertson (1963); UK | 6, mild<br>5, severe | Normal (1–3)<br>Normal (1–3) | — |

*Mild or severe according to the criteria of Lightwood & Stapleton (1953).
†Patients suffering from mild form of disease (R. G. Mitchell, 1962, personal communication).

The plasma and serum vitamin D activities recorded in samples from two p
with the benign form of the disease (R. G. Mitchell, 1962, personal communi
by Thomas *et al.* (1959) and by Cuthbertson (1963) on other similar p
were not significantly different from normal values or from values
mined on control patients, i.e. 1–3 i.u./ml. Similarly, in serum from a
suffering from the severe form of the disease, Lang & Eiardt (1957) found a
D activity of about 4 i.u./ml, i.e. a little above normal, as might perhaps ha
expected in this patient, who had received u.v. light treatment and daily
1000–10 000 i.u. vitamin D, apart from the administration of a total of 1 600
vitamin D in three separate doses during the previous 2 years!

The patients with the severe condition, reported by Fellers & S
1958*a*,*b*) and by Smith *et al.* (1959), present a different situation, in that
serum activities (Table 2) found were such as would only be expected to re
the administration of large amounts (more than 20 000 i.u.) of the vitam
The vitamin D intake of these patients, as reported by Fellers & Schwart
and by Smith *et al.* (1959), was in no way abnormal, ranging from about
5000 i.u./day and would certainly not be expected to have induced s
serum levels in normal patients. These results differ markedly from the

y Cuthbertson (1963) (Table 2) in a series of five patients with the severe pe of disease, i.e. suffering from mental retardation, systolic murmurs, teosclerosis and the typical 'elfin' facies. Plasma samples were not ob[illegible]d from ree of these patients until they had been on a diet free from added vitamin D- r a period of from 3 weeks to 6½ months; it is thus possible that the vitamin D tivity may have fallen during this period. Even so, had these patients resembled ose of Fellers & Schwartz (1958*a*) or of Smith *et al.* (1959), the vitamin D activity ould [illegible] have been elevated even after this lapse of time, for these authors noted levated serum activity from 6 months to 2 years after stopping the administration f vitamin D. Plasma samples were taken from the other two severely affected tients, in one instance before transfer to a diet free from vitamin D; the sample om the other patient was taken 10 days after removal of all sources of vitamin D om the diet. These two samples were both shown to have vitamin D actitities ithin the normal range and not to differ in this respect from control samples ayed at the same time.

The condition noted in the severely affected patients studied by Cuthbertson 963) cannot therefore be attributed to unusually large doses of vitamin D ecause these infants had received average amounts, from 1000 to 3000 I.u. itamin D/day) or to unusually high levels of circulating vitamin D (which could ave been brought about by abnormally effective absorption, by decreased elimina- on of vitamin D or by other means); they would seem best to be explained by an nusual sensitivity to doses of the vitamin normally quite harmless or to some her derangement in Ca metabolism. The severely affected patients observed in the SA by Fellers & Schwartz (1958*a*) and by Smith *et al.* (1959) all had exceptionally gh serum vitamin D activities, sufficient easily to account for the observed state these patients, not unlike that to be expected from chronic vitamin D intoxication; is thus not necessary to postulate any abnormal sensitivity to vitamin D in these tients. The high level of circulating vitamin D is, however, more difficult to plain; it could have arisen from undisclosed or unknowing administration of large ses of vitamin D before or during treatment, though it is unlikely that it would ve escaped notice. Even if it had occurred, the serum vitamin D activity would e, to judge from the work of Warkany *et al.* (1942), have been expected to remain vated for so long after removal of vitamin D from the diet. It may therefore be at certain instances of the severe form of idiopathic hypercalcaemia are brought out by a derangement of vitamin D metabolism that permits high levels of circu- ing vitamin D activity even when the subjects have received only average amounts om the diet (1000–5000 I.u./day). In patients with the benign form of the disease, studies on serum and plasma vitamin D activity (Thomas *et al.* 1959; Cuthbertson, 63) have shown the levels to lie within the normal range, so that the con- ion may be due to an unusual sensitivity to the vitamin. It is also possible, in th the severe and benign forms of the disease, that a derangement of Ca metabolism primarily responsible, in that the condition is associated with an unusually efficient sorption of Ca (Creery & Neill, 1954; Bonham-Carter *et al.* 1955; Morgan *et al.* 56), and that improvement follows reduction of the serum Ca levels, whether it



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is brought about by treatment with cortisone, EDTA or phytic acid, or simply by maintenance on a diet low in Ca (Morgan *et al.* 1956). The single observation on liver stores, in a patient suffering from the benign form of the disease (Cuthbertson, 1963) and a control patient, again supports the suggestion that vitamin D metabolism is not deranged. Both the hypercalcaemic patient and the control had been receiving 3000 i.u. vitamin D/day, the control up till the time of the patient's death, though the vitamin had been withdrawn from the diet of the hypercalcaemic patient about 1 month before death. The fact that rather less vitamin D activity was found in the patient's liver than in that of the control is thus not surprising in view of the small amounts of vitamin D found in the livers of animals not given large doses of the vitamin (Devaney & Munsell, 1935) and the known rapid rate of disappearance of vitamin D from the livers of animals given the vitamin (Heymann, 1957; Warkany, 1936, 1937; Quarterman *et al.* 1963). These observations on liver vitamin D activity, as on plasma and serum activities, have failed to demonstrate anything abnormal about vitamin D activities encountered in at least the benign form of idiopathic hypercalcaemia. Rat biological assays, which have been used in all the studies quoted, can throw no light on the suggestion by Thomas *et al.* (1955) that the abnormality may reside in the accumulation within the body, and the failure to eliminate it, of a vitamin D derivative, such as, for instance, dehydrotachysterol, which may have a potent effect on Ca metabolism in man and yet have little or no antirachitic effect in the rat. Further investigation is required to determine whether the disease may be due to an abnormal sensitivity to vitamin D, since these patients show toxic responses to doses closely similar to those commonly needed to ensure normal utilization of Ca, or whether the condition may be due to an error in Ca metabolism and so to a large extent independent of vitamin D intake, at least within the range of vitamin D intakes commonly encountered in this country.

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## Nutritional problems in the immigrant population in London

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During the past 10 years the immigrant population of this country has increased enormously. The three main countries of origin have been the West Indies, India and Pakistan. The immigrants largely settled in the big cities where they tended to aggregate in certain areas. In London, Brixton and Camberwell have a very high proportion of West Indian people. It is interesting to note that, although the number of immigrants entering this country has been greatly reduced as a result of the new immigration laws, the birth rate among those already here is very high. In Dulwich and St Giles Hospitals in London the number of West Indian babies born totalled over 1000 last year and is increasing annually. It is obvious that the number of immigrant people in the big cities will continue to increase and their medical problems should therefore be well understood. A few of these problems are genetically determined, such as sickle cell anaemia and thalassaemia, but these diseases are uncommon. Much more important are the problems related to the adaptation which has to take place of these non-indigenous people to their new country.

West Indian children are occasionally seen in our hospital with minor skin changes suggestive of deficiencies of vitamin A and the vitamins of the B complex. These changes are nearly always very mild and disagreement arises as to whether or not they are significant. Of recent years however two nutritional diseases have been described amongst immigrant children, namely iron-deficiency anaemia and rickets. Both these diseases occur with a frequency and severity which leaves no doubt that they are an important aspect of the health of the children of the immigrant communities. Nearly all the affected children were born in this country of parents who had immigrated here. In November 1960 attention was drawn to the high incidence of iron-deficiency anaemia among West Indian children in the Camberwell and Brixton areas of London (Davis, Marten & Sarkany, 1960). They investigated a total of 114 infants whose ages ranged from 5 to 23 months and of whom forty-seven were West Indian and sixty-seven were European. One of their interesting findings was that the weights of these children showed no statistical difference but the haemoglobin levels of the West Indians were significantly lower at all ages than those

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# The vitamin D activity of plasma of children with idiopathic hypercalcaemia

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Similarities between idiopathic hypercalcaemia of infants and vitamin D intoxication have led to the suspicion that the former may be caused by giving needlessly large doses of vitamin D to children who are more than usually sensitive to its effects or who absorb it with unusual efficiency. This view has been strengthened by the rarity of idiopathic hypercalcaemia in the USA and in Sweden, countries in which the vitamin D intake of children used to be much less than in the UK (Morgan, Mitchell, Stowers & Thomson, 1956).

In the USA Smith, Blizzard & Harrison (1959) reported a serum vitamin D activity of 23 i.u./ml in one patient, and Fellers & Schwartz (1958*a*, *b*) noted high activity, between 20 and 60 i.u./ml, in three patients. These findings support the view that idiopathic hypercalcaemia may be caused by overdosage with vitamin D. On the other hand, Thomas, Morgan, Connor, Haddock, Bills & Howard (1959) reported essentially normal vitamin D activities (1–3 i.u./ml) in samples of serums sent to the USA from patients in the UK. The work to be reported here was carried out further to investigate the condition in the UK.

## EXPERIMENTAL

*Samples.* Samples of heparinized plasma, 5–10 ml, from patients suffering from idiopathic hypercalcaemia were tested, together with similar samples obtained at approximately the same time from control patients of about the same age and sex but not suffering from any abnormality of calcium or vitamin D metabolism. All diagnoses were made by the physicians and pathologists named in the acknowledgements, to whom I am deeply grateful for providing the plasma samples.

In one instance, serum samples from the hypercalcaemic patient and from the control were provided but this mistake is not thought to have affected the results, because in other experiments no significant differences could be detected between the vitamin D activity of serum and plasma from the same specimen of blood. All samples were frozen quickly (to prevent protein separation) and stored in the deep freeze until assayed. Tests not reported here have shown that storage in a deep freeze for a period of several months, with melting and immediate refreezing at monthly intervals, or storage for up to 14 days in the refrigerator (4°) does not lead to loss of vitamin D activity. Livers from a child who died in idiopathic hypercalcaemia and from a control child dying from another condition were stored in the deep freeze until required. The livers were saponified by the method of E. Kodicek (personal communication). To each 50 g

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Table 1. *Plasma vitamin D activity and serum calcium level of children suffering from mild idiopathic hypercalcaemia and of control children*

(Numbers in parentheses denote days before (−) or after (+) transfer to diet low in Ca and vitamin D. NR, not recorded)

| Patient and sex | M.B., ♂ | E.F., ♀ | M.P., ♂ | H.K., ♀ | G.S., ♂ | S.W., ♀ |
|---|---|---|---|---|---|---|
| Date of birth | 14. iii. 62 | 9. ii. 59 | 27. iv. 61 | 13. xi. 61 | 17. iv. 61 | 9. ii. 59 |
| Date vitamin D withdrawn | 1. x. 62 | 14. x. 59 | 16. xi. 60 | 1. x. 62 | 25. x. 61 | 11. i. 60 |
| Date of introduction of diet low in vitamin D and Ca | 1. x. 62 | 30. x. 59 | 16. xi. 60 | 1. x. 62 | 1. xii. 61 | 8. ii. 60 |
| Approximate daily vitamin D intake before treatment (i.u.) | 1350 | 2000 | NR, probably 1000 | 2500 | 1000 | 2000–3000 |
| Serum Ca at or near date of diagnosis (mg/100 ml) | 12·9 (−14)<br>10·8 (−52) | 13·0 (0) | 11·4 (−5) | 13·2 (−4) | 11·5 (+36) | 13 (−80)<br>9·8 (0) |
| Serum Ca at or near date of vitamin D assay (mg/100 ml) | 12·9 (−14)<br>10·8 (+15) | 13·0 (0) | 10·4 (+9) | 9·4 (+15)<br>9·7 (+29) | 12·9 (+41)<br>12·4 (+43) | — |
| Plasma vitamin D activity (i.u./ml) | 2·9 (−2) | 3·0 (+3) | 2·0 (+7) | 2·1 (+25) | 1·5 (+42) | 1·4 (+140) |
| Plasma vitamin D activity of control patient (i.u./ml) | 2·3 | — | 3·0 | 3·6 | 1·7 | 1·1 |

Mean plasma vitamin D activity of patients 2·1 i.u./ml and of controls 2·3 i.u./ml.

Table 2. *Plasma vitamin D activity and serum calcium level of children suffering from severe idiopathic hypercalcaemia and of control children*

(Numbers in parentheses denote days before (−) or after (+) transfer to diet low in Ca and vitamin D)

| Patient and sex | A.C., ♀ | P.B., ♂ | A.B., ♂ | S.T., ♂ | S.D., ♀ |
|---|---|---|---|---|---|
| Date of birth | 15. v. 61 | 12. v. 59 | 17. iv. 61 | 26. ii. 61 | 26. iv. 59 |
| Date vitamin D withdrawn | 25. xi. 61 | 12. xi. 60 | 7. i. 62 | 11. xi. 61 | 17. x. 59 |
| Date of introduction of diet low in vitamin D and Ca | 25. xi. 61 | 9. xii. 60 | 7. i. 62 | 11. xi. 61 | 17. x. 59 |
| Approximate daily vitamin D intake before treatment (i.u.) | 1500 | 1900 | 1000 | 3000 | 1700 |
| Serum calcium at or near date of diagnosis (mg/100 ml) | 15·3 (−15)<br>16·1 (−11) | 11·7 (+3) | 11·4 (−1) | 14·9 (+3) | 14·7 (0) |
| Serum calcium at or near date of vitamin D assay (mg/100 ml) | 16·1 (−11)<br>11·7 (+9) | 11·8 (+11) | 9·5 (+17) | 13·4 (+16) | 8·3 (+190)<br>9·2 (+210) |
| Plasma vitamin D activity (i.u./ml) | 2·0 (0)<br>2·0 (+12) | • (+10) | 1·7 (+18) | 2·0 (+25) | 1·0 (+200) |
| Plasma vitamin D activity of control patient (i.u./ml) | 2·0, 2·0 | • | 1·7 | 2·0 | 1·0 |

Mean plasma vitamin D activity of patients 1·7 i.u./ml and of controls 1·7 i.u./ml.

• Statistical examination of the values from this assay showed that the vitamin D activity of the control and hypercalcaemic plasma did not differ significantly though the values were not sufficiently precise to permit a quantitative statement of vitamin D activity.

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of liver were added 30 ml absolute alcohol and 4 ml saturated aqueous KOH. The mixture was then heated for 30 min on a steam-bath and then allowed to cool. The digest was extracted four times with equal volumes of peroxide-free diethyl ether. The extracts were washed with water to eliminate alkali, dried over anhydrous sodium sulphate, evaporated and taken up in arachis oil. The extracts were diluted further with arachis oil and assayed by the routine line-test procedure as used for oily vitamin D preparations in these laboratories (International Union of Pure and Applied Chemistry, 1959) on forty-eight rats in each assay. The vitamin D activity of the plasma samples was also determined by the line-test rat assay method. Litters of four or eight rats were placed on the rachitogenic diet at 21 days of age. After 14 days they were divided into groups, each of at least six rats, matched for litter origin but otherwise randomly selected. The animals in two groups were each given, daily, either 0·1 or 0·2 ml of a standard arachis oil solution containing 2 i.u. vitamin D/ml, those in the other groups being all given, daily, 0·1 ml of arachis oil with either 0·05 or 0·1 ml of the plasma sample. All doses were given orally by syringe for a 10-day period, at the end of which the animals were killed, the tibias were dissected, and the degree of rickets was assessed by the line-test procedure. The vitamin D activity of the test sample was then calculated in terms of the standard.

Table 3. *Vitamin D content of liver from a child with mild idiopathic hypercalcaemia and from a child not suffering from any known derangement of calcium or vitamin D metabolism*

| | Hypercalcaemic child* | Control |
|---|---|---|
| Weight of liver (g) ... | 175 | 136 |
| Total vitamin D activity and fiducial range ($P = 0·95$) (i.u./liver) | 120 (50–150%) | 435 (43–1300%) |
| Vitamin D intake (i.u./day) | 3000 until 1 month before death | 3000 |

* First case described by Rhaney & Mitchell (1956).

Table 4. *Plasma vitamin D activity of children with different vitamin D (ergocalciferol) intakes*

| Child and sex ... | K.B., ♀ | P.H., ♂ | M.P., ♀ |
|---|---|---|---|
| Age | 15 months | 8 years | 9 years |
| Condition | Aminoaciduria | Cystinosis | Vitamin D intoxication |
| Ergocalciferol dose (i.u./day) | 1000 | 20000 | 150000 |
| Period of dosing before test | 8 months | 6 years | 20 months |
| Plasma vitamin D (i.u./ml) | 3 | ≃10 | > 20* |

* The activity of this sample could have been very much higher than indicated.

## RESULTS

The results obtained on examination of samples from six patients with the mild and five with the severe form of idiopathic hypercalcaemia are summarized in Tables 1 and 2 respectively, together with other relevant facts and the vitamin D activity of the samples from the control patients.

Table 3 provides information on the liver samples, and Table 4 on the results obtained on samples from three children with precisely defined vitamin $D_2$ (ergocalciferol) intakes.

## DISCUSSION

The results given in Tables 1 and 2 show that the vitamin D activity of all the samples examined fell within the range 1·0–3·6 i.u./ml, which is in close agreement with results of determinations made by Thomas *et al.* (1959) on normal subjects. Further, they show that the values for patients with the severe or the mild form of the disease do not differ from each other or from those for the controls. One of the patients, H.K., was a twin, and her twin sister was used to provide a control plasma sample. Both children were brought up and fed in the same way and given the same vitamin supplements until admission of the affected twin to hospital, except that for some time before entering hospital the affected twin had a poorer appetite.

In only five instances were samples obtained when the patient had been on a diet free from vitamin D for less than 10 days. It could therefore be argued that plasma vitamin D activity might originally have been high but that this activity had fallen in a number of the patients during the time they had been kept on the vitamin D-free regimen before assay. Had it been so, then the difference between the activities of samples from patients and controls should have been much greater for patients M.B., A.C., E.F., P.B. and M.P. than for the others who had been under treatment longer before examination. In fact, the values for these patients did not differ from those for their controls any more than did the others in this series.

Smith *et al.* (1959) and Fellers & Schwartz (1958*a*, *b*) showed that the high serum vitamin D activity noted in their patients with idiopathic hypercalcaemia fell only slowly after they had been transferred to a vitamin D-free diet. Warkany, Guest & Grabill (1942) and Thomas *et al.* (1959) have shown that serum vitamin D activity, once elevated by administration of vitamin D, may take several months to return to normal. Thus if any of the patients in this series had had significantly elevated plasma vitamin D activity before withdrawal of vitamin D, then this value would be expected still to have been higher than the control value for several months afterwards. In fact significantly higher levels were not noted in any of the patients in this series, so that it is unlikely that the condition in these patients could have been associated with a high plasma vitamin D activity.

This conclusion is supported by the figures in Table 3, which show that the liver stores of a child who died in idiopathic hypercalcaemia were in fact smaller than those of a child of the same age who had been receiving about the same amount of vitamin D. The hypercalcaemic child had not been given any vitamin D for 1 month before death. This fact could explain the lower vitamin D content of the liver, but the fact that the child was certainly suffering from idiopathic hypercalcaemia at death shows that a high vitamin D status is not necessary for demonstration of the condition. Unfortunately the vitamin D activity of the plasma could not be determined, but the liver vitamin D activity, about 1–2 i.u./g, was not much different from that expected in plasma from children of this type. Devaney & Munsell (1935) showed the vitamin D

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content of livers of sheep, cattle and pigs to be about 0·1–0·5 i.u./g, which is somewhat lower than the activity of serum (0·5–1 i.u./ml) found in the same species by Warkany (1937). More recently Quarterman, Dalgarno & Adam (1963) have shown in the pig that blood vitamin D activity is higher than that of the liver. Our findings may therefore indicate that in man, as in some other species, liver vitamin D stores are small, at least in individuals receiving moderate amounts of the vitamin.

Table 4 shows that 1000 i.u. vitamin D/day can maintain a plasma vitamin D activity of about 3 i.u./ml, doses of 20000 i.u./day can cause a marked rise in the plasma vitamin D activity, and administration of 150000 i.u./day causes a still further increase in plasma vitamin D activity. It appears that the plasma vitamin D activities found both in the idiopathic hypercalcaemic patients and the controls of this series are what would be expected from the vitamin D intakes of the children as calculated from the available information on the foods and vitamin supplements given to them. The results obtained agree with those reported by Thomas *et al.* (1959) for two mildly affected patients (R. G. Mitchell, 1962, personal communication) but differ markedly from those of Fellers & Schwartz (1958*a*, *b*) and Smith *et al.* (1959). The last two groups of workers reported high serum vitamin D activities in their hypercalcaemic patients (all of the severe type). My own observations do not support their hypothesis that an abnormality of vitamin D metabolism associated with an increase in serum vitamin D activity is a necessary prerequisite for the disease, though it may sometimes be so. A more likely explanation is an abnormal sensitivity in these patients to the toxic effects of vitamin D or an abnormality in calcium metabolism not caused by vitamin D. However this may be, the results show that in this series of patients the disease could not be attributed either to an unusually high intake of vitamin D or to an unusually high plasma vitamin D activity.

## SUMMARY

1. The plasma vitamin D activities of a series of eleven children suffering from idiopathic hypercalcaemia (five with the severe and six with the mild form of the disease) were found not to be significantly elevated in comparison with values determined at the same time on plasma samples from healthy children of like sex and age.

2. The vitamin D content of the liver of a patient dying with idiopathic hypercalcaemia was found to be lower than that of the liver from a control patient not suffering from any derangement of calcium or vitamin D metabolism.

I gratefully acknowledge the assistance of Dr J. A. Black, Professor D. V. Hubble, Dr M. C. Joseph, Dr R. Lightwood, Dr J. C. Macaulay, Dr R. G. Mitchell, Dr A. P. Norman, Dr K. Rhaney, Dr B. E. Schlesinger, Dr W. C. Smallwood, Dr R. H. Wilkinson and Dr B. S. B. Wood, who provided the plasma samples or permitted them to be obtained. I also wish to thank Mr G. W. Flynn and Mrs P. Charles for technical assistance.

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# HYPERCALCEMIA

## PART I*

J. H. FOERTSCH, M.D.

*A review of the literature indicates that hypercalcemia occurs more frequently than one suspects. The criteria for diagnosis are well established; however, detecting its clinical presence and determining its cause oft times taxes the skill of the most astute.*

### HISTORY—PAST AND PRESENT

CLINICAL IDENTIFICATION of the various hypercalcemic states necessarily originates from the anatomical identification and physiological knowledge accumulated from studies of the parathyroid glands.

In 1880 Ivar Sandstrom gave the first anatomical description of the parathyroid glands. Gley, in 1881, demonstrated tetany following removal of the parathyroids. Nine years later, von Recklinghausen described a bone disease which he felt was primarily osseous in origin and termed this pathological state "Osteitis Fibrosa Cystica." In retrospect, it appears that these cases probably represented the classical bone changes of long-standing, severe, hyperparathyroidism. Erdheim, in 1906, pointed out the relation between calcium metabolism and the function of the parathyroid glands. The original experiments of MacCallum and Voegtlin in 1908 proved that tetany occurring in parathyroidectomized animals was caused by a low serum calcium and was ameliorated by intravenous injections of soluble calcium salts.[1, 2]

In 1924, Felix Mandl in Vienna successfully removed a parathyroid adenoma in a patient suffering from generalized Osteitis Fibrosa Cystica. Albright[3] also described the first diagnosis and study of a patient with primary hyperparathyroidism by DuBois in this country and states that both of these patients had such extreme bone involvement that the skeletal structure was almost a gelatinous mass. As clinical observations continued and data relative to the clinical picture of hyperparathyroidism accumulated, there evolved an impression that bone disease was a primary manifestation of hyperparathyroidism. As observations were extended, parathyroid over-function was soon found to be associated with hypercalcemia, hypophosphatemia and hypercalciuria and the acceptance of a diagnosis was limited to these criteria.

In 1924 and 1925 Hanson and Collip further substantiated and amplified the work of Gley and Erdheim by preparing an extract of the parathyroid glands which contained an active principle of the parathyroid hor-

*Part II of Hypercalcemia will appear in the August issue of The Journal.



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mone. They demonstrated elevation of the serum calcium following injection of this hormone and ensuing animal studies tended to substantiate the presence of hypercalcemia, hypophosphatemia and the hypercalciuria as was reported in the earlier observations of hyperparathyroid activity in man.

Later it was realized that bone lesions need not necessarily be present in hyperparathyroidism, and the importance of nephrolithiasis was recognized so that many cases of parathyroid over-activity were diagnosed from the incentive projecting from the observations made [illegible] renal calcinosis. Further modifications in the criteria for the diagnosis of hyperparathyroid activity unfolded through the years so that it is now accepted that some patients have hyperparathyroidism without nephrolithiasis or bone disease and, more importantly, present only minimal chemical abnormalities.[4] It is now known that although an elevated serum calcium is still the most important single laboratory finding in this disease, the degree of elevation may be only slight.[5]

About 1928 it became apparent that there existed clinical states of hypercalcemia with no evidence of over-activity of the parathyroid glands. Hess and Lewis (1928) described the occurrence of hypercalcemia and hypercalciuria in patients given large amounts of Vitamin D. In 1929, Aub[7] and his associates reported a case of hyperfunction of the thyroid gland which was associated with hypercalcemia and increased excretion of calcium and phosphorous in the urine. Since this time there have been numerous case reports of elevated serum calcium occurring in hyperthyroidism and the presence of hypercalcemia has been documented in 19 cases.[8]

The diagnostic differentiation between hypercalcemia resulting from parathyroid over-function and hypercalcemia resulting from other etiologic factors progressed gradually. By 1931, the classical picture of hyperparathyroidism was well-defined,[9] and by 1955 about 750 cases of hyperparathyroidism had been reported in the literature, 97 per cent to 98 per cent of whom had either bone or kidney complications or both.[10]

In 1949, Albright and Reifenstein presented a list of the most-common clinical causes of hypercalcemia.[11] This list is presented in Table one, as amended by Huth.

TABLE ONE

1. Primary hyperparathyroidism
2. Sarcoidosis
3. Hyperthyroidism*
4. Neoplasm with skeletal lesions
5. Neoplasm without skeletal lesions*
6. Immobilization with, for example:
   (a) Paget's Disease
   (b) Paralytic poliomyelitis
7. Vitamin D intoxication
8. Milk Alkali Syndrome
9. "Laboratory error"

*Hyperthyroidism and neoplasm without skeletal lesions were not included in the original list of Albright and Reifenstein.

As Huth[12] indicates, this original list has grown only by the addition of hyperthyroidism and neoplasm without skeletal lesions. He further indicates that finding the cause of an elevated serum calcium has become an increasingly complicated procedure; for example, recently there has been reported, within the same patient, multiple causes for hypercalcemia such as hyperparathyroidism associated with Paget's Disease,[13] the case reported by Jackson, *et al.*,[14] and the case reported by Goldberg and his associate, Torack[15] in which a functioning parathyroid adenoma occurred with functioning hyperplasia of the parathyroid glands.

To the above list, we suggest that the following causes of hypercalcemia might be added: The hypercalcemia of infancy;[16,17,18] adenomatosis of the endocrine glands;[19,20] and the recently reported cases of hypercalcemia due to parathyroid adenoma supervening in circumstances of glomerular failure with stimulation of the parathyroid gland by the elevated serum phosphorus.[21]

Nordin[22] reports that he has seen two cases in which all the available evidence suggested that the primary lesion was pyelonephritis, yet a parathyroid adenoma was found at autopsy. He states, "it seems possible, therefore, that continuous stimulation of the parathyroid glands occasionally may lead to independent adenoma formation. These cases differ from the usual type of renal failure with secondary hyperparathyroidism in the very great severity of the Osteitis Fibrosa.

"The diagnosis of primary hyperparathyroidism in the presence of advanced renal failure is extremely difficult, if not impossible, owing to the depression of serum calcium which follows the elevation of serum phosphorus. However, theoretical considera-



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tions and actual observations suggest that depression of serum calcium by an elevated serum phosphorus does not occur until the latter has reached a level of about six or seven milligrams per cent. Hypercalcemia due to primary hyperparathyroidism should, therefore, remain detectable until this degree of renal failure has been reached, when it is very unlikely that removal of a parathyroid tumor would modify the course of the disease. The problem, therefore, is somewhat academic."

Since 1928 there has appeared a changing concept regarding the causes of hypercalcemia, taking root from the original demonstration of an elevated serum calcium as related to the over-production of parathyroid hormone. By 1949 other obvious causes had been recognized, as enumerated in the modified listings of Albright and Reifenstein, and as clinicians became more aware of the multiplicity of disorders capable of producing hypercalcemia, there appeared a parallel increase in the volume of explanations as to the mechanisms involved in producing such a state. These theories and concepts were altered and compounded by the appearance of more than one factor capable of producing an elevated serum calcium which developed simultaneously in one patient.

Today the field of calcium metabolism is once more in the realm of clinical and research interest, so that new concepts, new observations and new data are being fed into the stream of knowledge. Nevertheless, the factual information available still presents huge gaps which are slowly being closed by the accumulated accomplishments resulting from this resurgent interest.

Hypercalcemia is a polymorphic condition occurring in an assortment of benign and malignant states. It is now accepted as a fairly frequent occurrence and is not looked upon as the rare disturbance it was once considered. One wonders about the paucity of reports regarding parathyroid pathology in the literature of the earlier centuries, but a review of autopsy results discloses that frequently the parathyroids were not identified postmortem, for in many cases dissection of the neck in anticipation of possible parathyroid pathology was not done. Major[11] in his classic descriptions of disease does not devote any part of his book to the parathyroids nor to diseases involving calcium imbalance.

It is difficult to find any particular reason for the present revival of interest in the parathyroids and calcium metabolism. Two factors however, are probably most important in the renaissance: namely, the recent demonstration of the presence of parathyroid adenoma in the absence of renal changes and minimal chemical changes as reflected in the serum calcium and serum phosphorous levels, and the recent purification of parathyroid hormone which opened pathways to further advances in knowledge as it permitted the determination of the chemical structure, stimulated attempts to produce a synthetic preparation and opened the way for more definitive studies of the pharmacology and confirmation or rejection of present thoughts concerning action of the hormone upon bone, kidney, and other tissues. In addition, it may present the opportunity to modify or apply new diagnostic procedures and may disclose new therapeutic uses.

## SYMPTOMS AND SIGNS OF HYPERCALCEMIA

Although some confusion and variation of thought still exists regarding the mechanisms of the various hypercalcemic states, there is unanimity of opinion regarding the multitude of clinical disorders in which hypercalcemia may appear. Besides hyperparathyroidism, the classic cause of hypercalcemia, one series reported as many as 25 per cent of patients with advanced breast cancer,[12] another series of multiple myeloma cases reported an incidence of 40 per cent,[13] and 30 per cent of patients with sarcoidosis,[14,15] and slightly less than one-third of lung cancer.[16]

All observers agree that hypercalcemia can be nebulous, tending to escape detection and may well be called the "elusive evil-doer par excellence,"[17] but regardless of its origin it is injurious, dangerous and, if unattended, eventually lethal.[18] As a general rule, the injurious effects of hypercalcemia are prolonged and insidious so that in many instances the patient's symptoms have not yet reached the threshold of awareness. However, on occasion it can constitute a true crisis and precipitate sudden death.



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Hypercalcemic crisis is a rare occurrence. Thomas[11] reported three cases due to hyperparathyroidism and, as pointed out by Mieher,[12] crises can occur in any disease in which there is marked elevation of the serum calcium. During the crisis abdominal pain, persistent vomiting and marked dehydration occur. Serum calcium values may be as high as 19 or 20 milligrams per cent with phosphorus values of two to three milligrams per cent. Early in the course of the crisis there may be polyuria, but with the advent of dehydration oliguria and azotemia appear; marked muscular weakness and psychic disturbances become prominent features. Rehydration is necessary, and in cases where a parathyroid adenoma is present, surgical removal of the adenoma must be performed immediately.

Since the consequences of hypercalcemia are so formidable and the symptoms so vague and variable, what criteria exist that might arouse the physician's suspicion in any given case? In fact, the rise in the physician's suspicion index is in many instances the necessary antecedent before the diagnosis of hypercalcemia can be made.

The presence of hypercalcemia may be so hazy that Randall and Keating[13] speak of "Serendipity" in the diagnosis of hyperparathyroidism, implying that the condition is frequently discovered accidentally.

### GENERAL SYMPTOMS

Generally, one might become alerted by histories of weakness, weight loss, vague aches or stiffness in the joints and muscles, obscurely described by the patient and tending to make the physician label such individuals as "neurotic."[14] One should be particularly alert if the past history indicates a stable personality, who for no apparent environmental reason develops roving, general, indefinite symptoms. Keep in mind that the general symptoms may extend over a period of years; the important fact being the transplanting of symptoms to a formerly stable individual.

### RENAL CLUES

All patients with renal stones or a past history of renal colic, especially if stones were passed and found to be composed of calcium and phosphorus, should be thoroughly investigated. A review of patients attending a stone clinic, revealed an incidence of 16 per cent hypercalcemia.[15] In addition, all cases of polyuria should be checked for possible hypercalciuria and/or hypercalcemia. Occasionally, calcium casts are found on urine analysis, and this would indeed be a valuable clue.

### SKELETAL MANIFESTATIONS

This includes a very large group of patients, more women than men, in whom the ubiquitous radiological finding of osteoporosis demands concerted investigation as to etiology, because osteoporosis is merely a finding and in itself not a diagnosis. All x-ray changes showing non-specific demineralization of the bone with or without pain, all cases of spontaneous fractures, bone swelling, evidences of neoplasm with bone metastases and immobilized individuals, (especially in the first three to four weeks when bone resorption is at its height), such as children with casts or adults with Paget's disease or far-advanced osteoporosis, should be studied diligently.[16, 17]

### GASTRO-INTESTINAL SYMPTOMS

Of particular note are those duodenal ulcer patients who originally follow a medic regime and somehow feel worse. Then symptoms persist and the ulcer becomes intractable.[18] More evasive are the large number of patients who present vague digestive symptoms such as dryness of the mouth and throat, anorexia, nausea, vomiting, flatulence, disseminated abdominal pain as well as localized abdominal pain and constipation.

The diagnosis of hypercalcemia in this group is prone to escape, especially after

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thorough investigation of the G. I. Tract and evaluation of hepatic function fail to reveal intrinsic disease.

### NEUROLOGICAL SYMPTOMS

Many hypercalcemic individuals complain of fatigue and in addition may present central nervous symptoms of drowsiness, lethargy (which may advance to coma), confusion, memory loss, personality changes, impaired hearing or overt psychosis.[6]

A state of diagnostic alertness is particularly important in geriatric patients because there is an inclination to attribute neuropsychiatric manifestations of this type to the presence of cerebral arteriosclerosis.

Two other facets of the history remain important and are worthy of note: (1) up to the present time, 28 cases of familial hyperparathyroidism, (excluding cases of multiple adenomatosis), have been recorded in the literature;[7] (2) although infrequent, a history of vitamin D ingestion may provide the key to diagnosis.

### SIGNS OF HYPERCALCEMIA

There are no specific pathognomonic physical findings in hypercalcemia. Bone deformities and bone tenderness may be present and incite physician interest. A palpable mass in the neck may be of value, and suggest parathyroid adenoma, but many tumors appear in the neck so that this is non-specific; also, depressed or absent tendon reflexes, atonic or hypertonic muscles are likely signs, but still indecisive and inconclusive. Perhaps one of the most valuable physical findings may appear in the eyes.

### EYE SIGNS

In 1947, Walsh and Howard,[8] using a slit lamp, detected eye changes in over 50 per cent of their patients with hypercalcemia. Later, it was shown that visible eye signs may be present in the conjunctiva or cornea, or both, and in recent years the increasing clinical recognition of these eye signs, visible to the examiner's naked eye, have made it possible on occasion to diagnose hypercalcemia at the bedside.

In the ocular conjunctiva there may appear small, glass-like crystal-clear particles in the region of the palpebral fissure. These deposits may prove irritating, and in fact patients may present themselves complaining primarily of eye irritation, describing the eye symptoms as a burning sensation with increased lacrimation. In addition, the conjunctiva may be injected and inflamed.

Calcium deposits of the cornea produce a hazy, gray opacity, appearing as a slender, elongated, crescent-shaped form located in the limbus of the cornea on either the nasal or the temporal side, or both.[8]

The history and physical findings are, at their best, insufficient for diagnosis. However, their presence may produce a state of alertness in the physician as he probes the differential diagnoses which may evolve from the study of symptoms and signs presented by a patient. Laboratory and x-ray facilities provide additional aids once the possibility of hypercalcemia is considered. The establishment of its presence then poses the formidable problem of differentiation. Only by screening many possible etiologies, one by one, can the clinician define the given cause and, once having attained that state, attempt to apply necessary remedial measures. Most urgent, perhaps, is the differentiation of the hypercalcemia of hyperparathyroidism, which requires surgical intervention, from the other causes of hypercalcemia.

A survey of calcium and phosphorous metabolism with its interrelationship to bone and kidney focuses the mechanisms on which various clinical tests and differential procedures are based and necessary to establish etiology. A great deal has been written on the specific biochemical processes involved relative to specific changes occurring in many hypercalcemic states, but a great deal remains conjectural or theoretical.

### METABOLISM OF CALCIUM AND PHOSPHOROUS

The metabolism of calcium and phosphorous are intimately related to one another and coordinated with the metabolism of bone and renal function. The average 70 kilogram man contains about 1200 gms. of calcium and 600 gms. of phosphorous mostly in the



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free) bone."[5]

The average diet provides 0.8 to 1.5 gms. of calcium, the largest amount appearing in foods of dairy origin: Cheese contains 930 mg./100 gms.; cow's milk 100 mg./100 gms. The recommended daily requirement of calcium is one gram per day in the non-pregnant, non-lactating adult. Approximately 1.5 to 2.0 gms. of phosphorous are consumed per day; the non-pregnant, non-lactating adult requires a minimum of 0.9 gm./day. Unlike calcium, phosphorous is readily obtainable in diets adequate in other respects, because it forms one of the most widely distributed inorganic elements of common foods, appearing in good quantities in milk, other dairy products, meats, and fish. In fact, it would be difficult to ingest a diet deficient in phosphorous."

The availability of calcium and phosphorous to the body is determined in part by the degree of solubility and, hence, their ionization. The calcium of food may be in organic combinations with proteins and organic acids or as inorganic compounds of carbonate, bicarbonates, and phosphates. Phosphorous in foods may appear in the form of esters of phosphoric acid, in proteins, lipids, and carbohydrates, and in this form it is readily placed in solution by the digestive processes and absorbed. However, phosphates that occur as phytin, as in brown bread, are not absorbed. An insoluable form of phosphorous appears in cereal grain as Inositol Hexaphosphate; this is not absorbed because of the insoluble salt (phytin) formed when combined with calcium and magnesium."

Given an adequate diet, several factors influence the absorption of calcium. It is known that the ratio of calcium to phosphorous in the diet is important, for the optimum ratio for absorption of both elements is about 1:1 (calcium:phosphorous). In addition, the degree of concentration in the intestinal tract, the needs of the body for calcium and phosphorous, the intestinal acidity or alkalinity and the presence of vitamin D are contributing factors in the absorption of these two elements. Generally, calcium absorption is facilitated by a more acid medium as occurs in the upper intestinal tract; however, hyperacidity probably does not facilitate superabsorption of calcium."[6] Under normal conditions of gastric acidity, calcium salts are converted to the soluble chloride form. The acidity of the duodenum, normally pH 2.3-7.0 is also important in determining whether the more soluble calcium salts are formed (chlorides and acid phosphates) or the less soluble basic phosphates. The calcium chloride and acid phosphate forms are readily absorbed, and it appears that the greatest degree of calcium absorption occurs from the upper intestinal tract. Vitamin D promotes the absorption of calcium and phosphorous, especially enhancing calcium absorption from the distal ileum where the alkalinity is higher than in the upper intestinal tract; consequently calcium uptake is relatively poor. Kramer and Kanof summarized the role of vitamin D, stating, "little is known as to its action. In some mysterious manner it facilitates the absorption of calcium from the intestinal tract and deposits it as a phosphate or carbonate in osteoid and cartilage matrix."

The absorption of phosphorous, like of calcium, is enhanced by acids, interfered with by alkali and, unlike calcium, it is increased by an excess of fat and decreased by a high calcium diet. The soluble inorganic phosphate compounds are readily absorbed while the organic phosphate compounds first must be hydralized in the digestive tract and converted to inorganic phosphate for absorption.

Once calcium and phosphorous have been absorbed and enter the blood, they may be used in various metabolic processes, or they may be stored or excreted. The great storage facility for calcium and phosphorous is the skeleton. In a normal adult the amount of calcium and phosphorous that enters the skeleton is off-set by an equal amount that is released from it. A state of checks and balances (dynamic equilibrium) exists between the calcium and phosphorous of the body fluids and the bones of the skeleton.

Both calcium and phosphorous make contributions to the body economy. Calcium is necessary for the blood clotting sequence, and ionic calcium influences the strength of the heartbeat, as well as the transmission of nerve impulses and influences skeletal muscle irritability, but it appears that these phenomena do not require maintenance of a calcium concentration within a severely-held narrow limit. Phosphorous plays a central role in the conservation and transfer of en-



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ergy in the intermediate metabolism of carbohydrates, proteins, fat enzymes and is quite important in the body's buffering system, dedicated to the maintenance of hydrogen ion concentration.[14, 15]

Within the blood, calcium is in solution in the plasma. In 1913, Rona and Takahashi[16] demonstrated two major and roughly equal fractions of serum calcium, the diffusable (ionized) and the non-diffusable (un-ionized) portions. The diffusable fraction is a solution of partially ionized, weak electrolyte calcium proteinate. The non-diffusable portion is firmly bound with plasma protein. The ionized and un-ionized fractions are in equilibrium with one another. The ionized fraction is directly under the influence of the parathyroid hormone and is physiologically active, being free to diffuse into other extra-cellular fluids.

Fajans[1] has emphasized that the total serum proteins are essential in the interpretation of clinical serum calcium levels. The ordinary clinical laboratory does not measure ionizable serum calcium but reports the TOTAL serum calcium. Therefore, it is most important for the clinician to know the level of the serum proteins when studying the serum calcium. In addition, the physician should be aware of the normal range of serum calcium in the laboratory employed. It has been suggested that the range of nine to 11 mg. per 100 cc. as normal values for serum calcium has been pegged too high.[14, 15] In any event, if the total serum proteins are normal a serum calcium of 10.5 mg. per 100 cc. should serve as an alert, indicating that further studies of the calcium-phosphorous metabolism of that patient should be undertaken. On the other hand, if serum proteins are depressed, a level of 10.5 mg. per 100 cc. may be definitely elevated and indicate hypercalcemia; less of the total serum calcium would be in protein-bound form and relatively more would be in ionizable form.

Phosphorous exists in the blood in four main forms: Inorganic phosphorous (orthophosphate) and three organic combinations —ester phosphorous, lipid phosphorous, and nucleic acid phosphorous.[17] Like calcium, the inorganic phosphate values of blood plasma have been challenged. Vigorous investigation of phosphorous serum levels requires a deviation from the previously accepted values of three to 4.5 mg./100 cc in adults and from 4.5 to 6.5 mg./100 cc. in children. Greenberg, Winters, and Graham[18] feel that the accepted values for serum inorganic phosphorous concentrations have never been established adequately, and have been able to demonstrate that both age and sex affect the serum phosphorous level and must be taken into account in making diagnostic decisions (see figures 1 and 2). It is therefore important that each laboratory establish its normal values for serum phosphorous for each sex at various ages. It is known also that serum phosphorous decreases during periods of increased carbohydrate utilization and ingestion of large amounts of calcium or the parenteral administration of magnesium.

The non-lactating adult excretes the largest fraction of calcium in the feces as a component of intestinal juices, only a small portion appearing in the urine. The urinary mechanism for calcium excretion is not well-understood. In a normal adult, the serum threshold for urinary calcium is about seven mg./100 cc. The ionized portion of serum calcium passes readily through the glomeruli and appears in the glomerular filtrate. This increases the ionized calcium and increases proportionately that amount which appears in the glomerular filtrate or vice versa. There appears to be a limit to the glomerular filtration capacity for calcium, and should this be exceeded it is reflected in a rise of serum calcium. Tubules of the kidney nor-

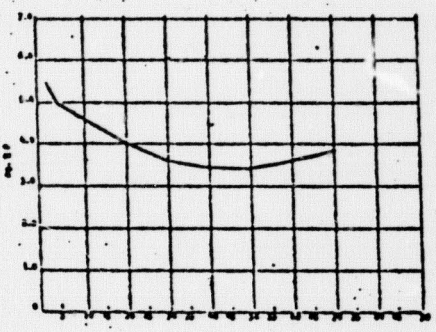

Figure 1.
Age in Years
Serum Phosphorous for Females



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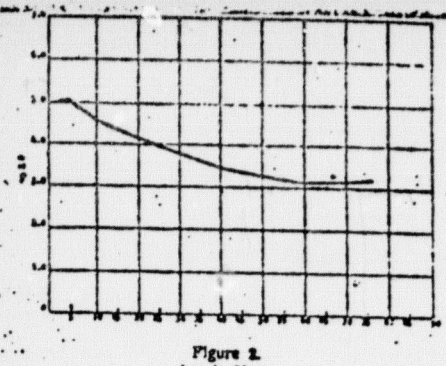

Figure 2.
Age in Years
Serum Phosphorous for Males

mally reabsorb about 99 per cent of the filtered calcium; the total amount reabsorbed varies directly with the amount filtered by the glomeruli.

Hypercalciuria can be produced by three mechanisms: An increase in the amount of calcium filtered by the glomeruli, a decrease in the renal threshold, or by an increase in parathyroid hormone.[5,6] Albright[7] reported that in hypercalcemia with hypercalciuria, calcium casts may be formed in the renal tubules and extruded into the urine.

Unlike calcium, the largest portion of phosphorous is excreted in the urine with only a small quantity appearing in the feces. Like calcium, a great deal of phosphorous can be excreted in the milk during lactation. In urine, phosphorous appears in the inorganic form (92-96 per cent), the remaining portion appears as unsplit ester phosphates. There does not appear to be a serum threshold for the glomerular filtration of inorganic phosphorous. Thus, all of the inorganic phosphorous passes through the glomeruli in the absence of renal impairment; there is no limit to the glomerular filtration capacity. The tubular reabsorption of phosphorous depends on the quantity of parathyroid hormone present. The administration of parathyroid hormone decreases the tubular reabsorption of phosphorous and greater amounts appear in the urine. In hyperparathyroidism, a decrease in the serum concentration of inorganic phosphorous occurs (since tubular reabsorption of phosphorous is reduced) and an increased amount of phosphorous consequently appears in the urine. Also, in the normal individual with an unusually high phosphorous dietary intake, all other factors being equal, there is an increase in urinary phosphorous excretion.[8]

## BONE METABOLISM AND PARATHYROID HORMONE

The formation of bone involves the laying down of a protein matrix and deposition of calcium phosphate crystals into the mass of protein tissue. The osteoblasts appear to produce this organic protein matrix (osteoid) and increased osteoblastic activity is reflected by elevated serum alkaline phosphatase levels. The proper mineralization of osteoid tissue requires calcium and phosphate ions at the site in a concentration equal to the proportion of calcium and phosphate in the mineral matter of bone. In an unknown manner, calcium and phosphate ions combine and precipitate in the form of angularly-shaped crystals which assume a definite pattern upon the matrix. This calcium phosphate salt crystal appears to be hydroxyapatite with the formula $Ca_{10}(PO_4)_6(OH)_2$. The growth of mineralization is continued layer upon layer, thereby the exposed surface of the moment becomes entrapped in the enlarging mass. Bone crystals in the body, if laid out, would cover a 400 acre area. The final calcified bone mass presents three types of surfaces: (1) a surface upon which nothing appears to be happening; (2) a surface upon which bone is being formed; (3) a surface upon which bone is being reabsorbed.[9,10,11] It has been accepted that the parathyroid gland regulates the calcium-ion concentration of the blood plasma and that there appears also to be an additional influence on the control of the blood phosphorous. These changes are effected through calcium supplied by the diet, the bone reservoir and renal function. Observers differ in their interpretation of how these mechanisms are accomplished and at present all the evidence is not available concerning the function of the parathyroid hormone.

The parathyroid glands appear as four flattened, oval discs measuring about three to four mm. in width and six mm. in length, arranged in two superior and two inferior position at the posterior edges of the lateral lobes of the thyroid gland.[12] In addition, numerous parathyroid glands may be scat-



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tered through the fat and connective tissue of the neck. These glands are endocrine in nature and produce a hormone, appearing to be free of the influences of the pituitary gland as evidenced by serum calcium, phosphorous studies in patients with hypopituitarism and from facts accumulated from experimental animals and humans after the performance of hypophysectomy.

The current concepts of what role the hormone of the parathyroid glands plays in the metabolism of calcium and phosphorous stems from three sources. The first of these is based on measurements conducted in the parathyroidectomized experimental animal or by the accidental extirpation of the parathyroids by thyroid surgery in humans. The second set of observations have been derived from cases of spontaneous hyperparathyroidism, and the third and final source of facts derives from experiments using parathyroid extract which contains active parathyroid hormone.[1] Greenwald[2] in 1925, observed that parathyroidectomy was followed by diminished output of phosphorous in the urine. Albright and Ellsworth[3] in 1929 introduced the concept that the calcium ion per 100 cc. times the phosphorous ion per 100 cc. (the solubility product) is approximately constant when all factors affecting calcium and phosphorous metabolism are constant except for the amount of parathyroid hormone present. This theory, derived from observation of a hypocalcemic, hypoparathyroid patient, stated that the serum inorganic phosphate was high and that a single injection of parathyroid extract caused a rapid rise in urine phosphate. Continued treatment of the patient with parathyroid extract resulted in a gradual fall in serum phosphate as well as a rise in serum calcium. As phosphate loss in the urine increased, plasma phosphorous decreased. The decreased serum phosphate in turn modified and changed the calcium times the phosphorous product of the plasma; this in turn permitted increased calcium resorption of bone, resulting in a rise of serum calcium.

In 1939, Albright and Reifenstein[4] modified this hypothesis by stating that the primary effect of parathyroid hormone was exerted upon some phase of phosphate metabolism, whether it be renal or extra-renal. The effect of the serum calcium was still held to be secondary.

Thomson and Pugsley[5] in 1932 proposed another view, stating that the parathyroid hormone acts directly on bone, resulting in resorption with liberation of calcium into the blood.

In 1948, Barnicot[6] and Chang[7] in 1951, presented evidence that the parathyroids act directly on bone. In experiments transplanting parathyroid glands onto the parietal bones of the skull in mice, it was noted that a marked local reabsorption of bone immediately beneath the graft occurred. In 1954, Grollman,[8] using peritoneal lavage to maintain blood chemistries within physiological limits proved that parathyroid extract when injected increases the serum calcium in nephrectomized animals. Thus, a recapitulation of the facts derived from experiments through the years of 1948 to 1954 demonstrates that the parathyroid hormone acts directly on bone and that it is capable of raising serum calcium in the absence of the kidneys. The observation of the effects of the parathyroid hormone on phosphorous and how these changes affected the serum calcium appeared after the year 1954.

The stimulus for conducting these experiments was provided by the recent purification of the parathyroid hormone with its attendant increased potency. Collip[9] and Hanson,[10,11] working independently in 1925, prepared the first physiologically active extract. Recently a high degree of purification of this extract has been achieved. The potency of the present product is reported to be 2500-3000 units per mg. It has a molecular weight estimated to be 7000 (±1500) and upon analysis proves to be a protein.[12,13] Copp[14] in his discussion of the possibility of whether there may be two parathyroid hormones (one which primarily affects bone, and one which primarily affects kidney), contends that the confusion has occurred from the very large doses of the commercial extract (used prior to the purified extract), and that some contamination side effects due to foreign constituents in the commercial extract occurred.

Munson and Iseri[15] recently have shown in the parathyroidectomized rat that the serum inorganic phosphorous failed to rise before the fall in serum calcium. Thus, the tenets of Albright's hypothesis (i.e. a rise in



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serum phosphorous due to increased tubular reabsorption of phosphorous must occur before a fall in the serum calcium takes place, thus altering the product of calcium milligrams per 100 cc. times phosphorous milligrams per 100 cc.) were not met. Munson then injected parathyroidectomized rats with parathyroid extract subcutaneously. The absorption of the hormone by this route is delayed and does not prevent the fall in serum calcium and phosphorous which occurs within two hours after removal of the parathyroid glands. At the end of six hours he found both the serum calcium and serum phosphorous levels of these animals had returned to preoperative levels; while the control rate, (i.e. parathyroids were removed but controls were not given parthyroid hormone) progressed to tetany and death within six hours. The rise in serum calcium which occurred in animals given the subcutaneous injection of parathyroid hormone was not accompanied by a fall in the serum phosphorous. Here again, Albright's principle was not confirmed, for the serum calcium rise should have been preceded by a decrease in the serum inorganic phosphorous, as the parathyroid hormone decreased tubular reabsorption of phosphorous, increasing the urinary phosphate and thereby lowering the serum phosphorous. Munson[7] points out that the effect of the hormone was to return both the calcium and the phosphorous to normal; he concludes that in man as well as in the rat the effect of parathyroidectomy and of parathyroid hormone on the level of serum calcium is not dependent on a prior change in the circulating level of inorganic phosphorous. Therefore, from the experiments of Munson one can conclude that most likely the primary target tissue of the parathyroid hormone for regulation of the level of circulating calcium is bone rather than the kidney and that whatever effects the hormone may have on phosphorous metabolism are probably of secondary importance.

Therefore, it appears that the parathyroids are sensitive to the calcium concentration of the plasma and that a falling level of calcium ions stimulates the output of parathyroid hormone. The hormone in turn increases the mobilization of calcium from bone (by direct action), thereby raising the calcium level of the plasma and that this method is one of self-regulation. McClean[10] describes the method of self-regulation as a "feed-back" mechanism. He defines this further by stating that in this system information about the out-put is fed back to an earlier stage, to modify the action of the earlier stage and thus effect a change in the out-put itself.

The effects of parathyroid hormone upon serum phosphorous (thought to be of secondary importance) are not clearly defined. It is fairly well-agreed that the rapid rise in urine phosphorous after an injection of parathyroid hormone indicates that the effect upon the kidney is direct, but the precise biochemical mechanism involved remains obscure. The confusion reigning now is illuminated by the fact that Nicholson[20] advanced experimental evidence indicating that the principle mode of action of this hormone on the kidney is to stimulate active excretion of phosphorous by the distal tubule and not, as is usually assumed, to inhibit the reabsorption of phosphorous by the proximal tubules. Because of this confusion, it has been postulated that the parathyroids are capable of producing two hormones, one affecting calcium metabolism per se, and the other influencing only phosphorous metabolism. □

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AT FIRST GLANCE, the title of this discussion may seem to be directed only to a somewhat limited segment of the medical profession. Quickly we may pass this by, thinking to ourselves, this does not apply to us, this is not a part of our routine work; but much to our surprise, statistically we find a large per cent of amputations done by the general surgeon and the general practitioner, well equipped and qualified to do this surgery. Perhaps we find more of this done by the above men due to the great strides in training, the increase in facilities for proper hospital and nursing care, the economic necessity of preserving and protecting the financial status of the patient, and particularly because of the emergency factor so often important following trauma and accidental injury due to our mechanical age.

If a short review of the more modern and basic methods of prosthetic fittings would avoid reamputations, then we feel the economic savings which follow to the individual and to the community at large would well justify our considerations. Therefore, in making and fitting artificial limbs, the one and only endeavor is to make certain that they are comfortable, functional, acceptable in appearance and as reasonable in cost as possible. This fitting by the prosthetist depends upon his individual skill, the type of limb required, but equally important to him and to the patient is the site of application.

Since this agency furnishes such a large per cent of such appliances to the medically indigent, we are particularly and necessarily involved in these problems.

Since World War II, giant strides have been made in the use of plastics and aluminum for artificial limbs. The National Research Council has participated actively in this work, enlisting the help of the airplane and missile industry in making these improvements. All of this has given better manufacturing techniques, lighter and more comfortable appliances and a greater ease of fitting areas of the body that in the past were unacceptable to the prosthetist.

In the upper extremity practically any length of stump can be well fitted. We must always remember that even a small stump, below the elbow or shoulder is in general much better than a simple disarticulation, although many disarticulations can be fitted satisfactorily. The short stump, when it can be preserved, gives much improved muscular control and consequently better use of the prosthesis.

In the lower extremity in general, amputations in the lower one-half of the tibia and be preserved, gives much improved muscular control and consequently better use of the prosthesis.

When possible, the preservation of length of the stump is very important. To produce a better, well shaped, well padded painless stump suture or reinsertion of muscle to end of amputation rather than tendon insertic and tying of all severed nerve ends with n absorbable suture, as silk or cotton, lo the formation of tender and painful neuromas. By re-attaching muscles with proper tension, closing deep fascia and other deep structures layer by layer and everting skin and superficial tissue, we may avoid many scar troubles.

Special training courses are available at University of California, Los Angeles, Northwestern and New York University for help and assistance to all the professions in the newer methods of fitting artificial limbs.

Here in Oklahoma, we have Amputee Clinics for adults and children at the University Medical Center. This is composed of an Amputee Clinic team, consisting of an orthopedist, physical therapist and prosthetist. This is available to the members of the medical profession for the proper fitting of artificial limbs. The staff men serve without remuneration and the patient is then returned to his attending physician. A nomin charge is made for this service.

A great deal of credit must be given to my many dedicated colleagues for their kind assistance, advice and constructive criticism. Through such interchange of ideas, we feel continued progress will be made in this all important work.—*Francis E. Dill, M.D., State Medical Consultant, Vocational Rehabilitation, Oklahoma City, Oklahoma* □



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# Clinical Nutrition

Second Edition · By 23 Authors

Edited by Norman Jolliffe, M.D.

*Foreword by W. Henry Sebrell, M.D.*

*with 137 illustrations, 61 in full color*

1962

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# BURNETT'S SYNDROME

Burnett and his associates[9] have emphasized that administration of both large quantities of milk and of alkali over many years may lead to metastatic calcification of subcutaneous tissue and visceral organs, especially of the kidneys. Under these circumstances, hypercalcemia with hypocalciuria, often accompanied by milk alkalosis and metastatic calcification, develop. Hyperphosphatemia is commonly a part of this syndrome, due in part to the tendency to uremia and in part to the high phosphate content of the milk. This indicates that not only the calcium but also the phosphorus of the milk must play a role in the production of this syndrome. Ultimately, marked renal insufficiency with azotemia ensues, and in this stage the alkalosis is replaced by acidosis. Amorphous calcium masses are deposited in the subcutaneous tissue, mainly in the neighborhood of the articulations in the synovial membranes, and even in tendons. The calcium deposition often also involves the kidneys, stomach, blood vessels, dura mater, falx, diaphragm, and the respiratory tract. The presence of band-shaped keratitis or keratopathy can frequently be elicited by slit-lamp examination.

The urinary calcium excretion is nearly always within normal limits and is often even low. The alkaline phosphatase of the serum is normal; anemia is usually present. If this syndrome is discovered in an early stage, the onset of uremia may be prevented by the cessation of milk and alkali ingestion. However, at least one patient with Burnett's syndrome expired one year after milk and alkali administration had been eliminated.

The differentiation of this condition from hyperparathyroidism may be difficult.[3] The latter disease must be diagnosed in all cases in which generalized osteitis fibrosa, giant cell tumors, and other skeletal anomalies, hypophosphatemia and hypercalciuria are present. In Burnett's syndrome the subcutaneous calcium deposits are much more extensive than in patients with hyperparathyroidism. The diagnosis of Burnett's syndrome should not be made unless there has been a high alkali intake for many years, with or without a high calcium intake. Prompt improvement should be obtained on cessation of treatment with milk and alkali. Finally, marked resorption of bone, and especially the presence of osteoclastomas, militate against the diagnosis of Burnett's syndrome.

The excess of alkalinizing agents is, in the opinion of the author, a more important factor in pathologic calcification due to dietary causes than the ingestion of excessive quantities of calcium salts.[32]

The question has been raised whether metastatic calcification develops especially in ulcer patients whose kidneys were damaged before the milk diet and alkali administration had been started. In this connection, the interesting observations of Swyer and his associates[31] on hypercalcemia in patients with osteolytic skeletal metastases after androgen therapy should be mentioned. At autopsy, such patients nearly always show signs of pre-existing renal disease. Similarly, it seems possible that calcinosis, hypercalcemia, and uremia are more likely to develop when patients treated with alkalies and/or a Sippy regime have pre-existing renal disease.

## HYPERVITAMINOSIS D

In recent years, patients with rheumatoid arthritis, children with vitamin D resistant rickets, and, in Europe, patients with lupus vulgaris have been treated over periods of several weeks or months, sometimes even years, with daily doses of calciferol equivalent to 500,000 I.U. of vitamin D. Massive doses of vitamin D influence bone resorption more than calcium accretion.[11] Thus, in hypervitaminosis D the common signs are hypercalcemia, hyperphosphatemia, and hypercalciuria. The alkaline phosphatase of the serum remains normal. In addition, marked and generalized resorption of bone develops, together with metastatic calcification in kidneys,[71] blood vessel walls, gastric mucosa, heart, lungs, sclerae, falx, dura mater, thyroid, pancreas and periarticular soft tissues.[37] Band keratitis due to calcium precipitation in the cornea deserves special mention.

Metastatic calcification in the kidneys can often be visualized on the roentgenograms in the form of nephrocalcinosis limited to the medullary pyramids and the renal pelvis. In some cases the calcium deposits in the kidneys remain microscopic in size and do not show up on the x-rays, but the albuminuria and the impairment of the kidney function may be just as serious as when grossly visible nephrocalcinosis is present. Renal stone formation has also been observed. Ultimately, metastatic calcification of the kidneys always leads to uremia.

It is of great importance to recognize hypervitaminosis D as the cause of uremia because, after cessation of the vitamin D intake, calcium and phosphorus both of serum and urine go down to normal levels and the renal function improves. The resorption of small calcium deposits near the interphalangeal joints may take one year. Larger para-articular deposits remain unchanged for a much longer period.

In general, hypervitaminosis D needs to be differentiated from hyperparathyroidism and Boeck's sarcoidosis. In hyperparathyroidism, hypo-

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phosphatemia often occurs, while in hypervitaminosis D and in sarcoidosis the serum phosphorus is usually slightly increased. In renal osteodystrophy the serum calcium is nearly always low, or at best normal, the serum phosphorus is high, the urinary calcium and phosphorus excretion are decreased.

Since the dangers of the administration of excessive doses of vitamin D are common knowledge, hypervitaminosis D in adults has become a rarity. However, in infants, at least in the United Kingdom, a new syndrome, "idiopathic hypercalcemia," has now been recognized which may well be due to hypervitaminosis D. A recent report mentions that between 1953 and 1955, 205 such patients, mainly infants between 4 and 8 months of age, have been observed.[7]

In the malignant form of this disease, dwarfism, mental retardation, microcephaly and cerebral signs are present. The benign form of the disease is reversible and is of considerable clinical importance.[12] Children with benign idiopathic hypercalcemia usually suffer from loss of appetite, tenacious vomiting, and constipation. Often, a systolic murmur can be heard, either at the point of maximal impulse or all over the precordium. Hypercalcemia and hypercalciuria are constant findings; the serum phosphorus and alkaline phosphatase usually remain normal. Blood urea nitrogen and cholesterol are increased. Under adequate treatment these abnormal values rapidly return to normal and the systolic murmur disappears.

Nephrocalcinosis has been frequently observed. Linear disposition of abnormally dense bone near the epiphyses of the long bones and osteosclerosis of the skull base and vertebral bodies may be present.

There is strong evidence that hypervitaminosis D played an important role in the etiology of this idiopathic hypercalcemia of infants.[6,7,9] "National Dried Milk," a popular food for infants in the United Kingdom, contained "not less than" 1,200 I.U. of vitamin D per reconstituted liter, and probably more. The vitamin D content of several other milk preparations used for infant feeding in England was even higher. The "British National Cod Liver Oil Compound" contained not less than 700 to 800 I.U. of vitamin D per teaspoonful, and probably more. Cereals were also fortified and some brands contained 1,500 I.U. per ounce. Infants who received 1.5 pints of reconstituted dried milk, 1 ounce of fortified cereal, and one teaspoon of fortified cod liver oil ingested about 4,000 I.U. of vitamin D per day. This intake was far in excess of the dose of 400 to 700 I.U., which around 1940 was recommended as the daily intake for infants. The daily maximal intake of vitamin D for infants was usually considered to vary around 1,500 I.U.

In this connection, it is of interest that in the United States only a few cases of idiopathic hypercalcemia have been reported. In this country the most popular brand of evaporated milk contains only 420 I.U. of

vitamin D per reconstituted liter. However, the possibility exists that cases of hypervitaminosis D in infants and children may also develop in the United States, since certain halibut liver preparations used in this country contain 6,000 I.U. vitamin D per teaspoonful.

Breast feeding has not become obsolete in England, and it is interesting that until now no case of idiopathic hypercalcemia in a breast-fed infant has been reported. The vitamin content of human milk varies between 50 and 100 I.U. vitamin D per liter, that is, only 25 per cent of the vitamin D content of vitaminized cow's milk.

In most cases of idiopathic hypercalcemia, feeding with low-calcium milk powder (Locasol) and low-calcium cereal (Glaxo) boiled in distilled water brings rapid recovery. In other cases, cortisone, mainly by inhibiting calcium and phosphorus absorption from the intestine, has been helpful.

The British Pediatric Society decided to recommend that no food fortified with vitamin D should be given to infants. Every infant, however, it was stated, should receive cod liver oil of known potency. This, of course, is exactly the same nutritional formula customary half a century ago.*

Idiopathic hypercalcemia in older individuals who do not receive excessive amounts of vitamin D with their food[14] may be due to insufficient inactivation or elimination of vitamin D.

## OTHER DISEASES OF THE SKELETON IN WHICH CHANGES IN CALCIUM AND PHOSPHORUS METABOLISM OCCUR

In Paget's disease of the bone and in hyperthyroidism, hypercalciuria in the presence of normocalcemia is common.[40] The alkaline phosphatase content of the serum is increased in the former, normal in the latter malady.

Hypercalcemia and hypercalciuria often occur in widespread malignancies, in rapidly progressive cases of multiple myeloma, and also in lymphomatous disease, usually when extensive skeletal involvement is present. In contrast, in a patient with adenocarcinoma of the lung and widespread osteoblastic lesions, hypocalcemia has been observed.[42]

In sarcoidosis, with or without skeletal lesions, hypercalcemia and hypercalciuria may occur.[10,41,48,55] In this disease the intestinal absorption is remarkably high. Actually, the calcium content of the stools may dwindle to traces. After administration of corticosteroids the intestinal

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GENERAL MEDICINE

# Hypervitaminosis D for arthritis —A Case Report

*Hypervitaminosis D results from a greatly excessive intake of vitamin D over a prolonged period of time. The patient whose case is reported received 200,000 units of vitamin D daily for 12 years.*

## Case Report

R.G., a 41-year-old judge, was admitted to the Martha Jefferson Hospital on December 28, 1962 with the complaint of chest pain of seven days duration. He described the pain as a severe sharp discomfort around the postero-lateral chest with aggravation by deep breathing. The pain had come on suddenly one night and had remained severe for four days. It had been less severe for 48 hours prior to admission, but approximately 24 hours before coming to the hospital he had some hemoptysis. He had no fever.

Just 22 days before the present admission, the patient had been hospitalized and treated for a calculi of the urinary bladder, benign prostatic hypertrophy, and contracture of the vesicle neck. He had a cystolitholapaxy and a transurethral resection of the prostate gland and was discharged four days before the present admission. During this hospitalization his urine was cloudy yellow with a specific gravity of 1.011 and a pH reaction of 5. There was a trace of albumin; negative sugar; and on microscopic 8-10 WBC/hpf and 12-15 RBC/hpf. The blood urea was 46 mg.%. The serum calcium was 11 mg.% or 5.5 mEq/liter and the serum phosphorus was 3.2 mg.% or 1.9 mEq/liter.

The past history was significant for diphtheria as a child. In 1945 he began to have back pain and was diagnosed as having Marie-Strumpell arthritis. The arthritis became worse in 1947 and he received radiation therapy to the back at Walter Reed Hospital. In 1950 he was placed on vitamin D, 50,000 units four times a day, and had taken this medication regularly for the past 12 years. He also had been taking one grain of thyroid extract a day and had been placed in a three-point brace for his back. In 1957 he had had a thrombo-

This work was done on the Medical Service of the Martha Jefferson Hospital, Charlottesville, Virginia.

phlebitis of the deep veins of the left leg and was hospitalized at the Martha Jefferson Hospital for two weeks of treatment. Since the time of this phlebitis he had had a post-phlebitic leg with enlargement and some edema. The urinalysis revealed a specific gravity of 1.020; albumin negative; sugar 1+; acetone negative; and microscopic revealed a few epithelial cells and 16-18 WBC/hpf. There were some calcium oxylate crystals in the urine. The urine Sulkowitch test was slightly increased. The serum calcium, serum phosphorous, and alkaline phosphatase were normal. The PSP test yielded the following results: 30 minute urinary output, 78 cc. and 35% excretion; one hour, 66 cc. and 35% excretion; two hour, 78 cc. with 10% excretion; and a total output of 222 cc. and 70% excretion.

In 1958 he developed bladder calculi requiring cystoscopy and stone crushing at the University of Virginia Hospital. A review of his records at this time revealed that calcium metabolic studies were not done. The urinalysis, however, revealed a specific gravity of 1.014; albumin trace; sugar negative; and a microscopic with 20-25 WBC/hpf, innumerable RBC/hpf, and no casts.

The family history revealed that his mother had had diabetes.

The systems review revealed a nocturia of two times, some frequency, polyuria, dysuria, and polydipsia. There was no anorexia. He did fatigue easily.

On physical examination, he was alert with a stooped poker back and his head deviated to the right. He was not in acute pain at the time of examination. Blood pressure was 160/90; pulse 84; temperature 97.8°. Examinations of the eyes, ears, nose, throat, lymph glands, and heart were normal. The chest revealed hyperresonance with dullness and rales at the right base. The abdomen was encroached on by flexion of the back so that the iliac spines reached towards the lower rib cage. There were no masses felt in the abdomen. The femoral, dorsalis pedis, and posterior tibial pulses were normal. The left leg was larger than the right leg with superficial varicosities. There was no calf tenderness and the Homan's sign was negative. There were no rectal masses and the prostate was slightly enlarged.

The urine was clear with a pH of 5.0 and a specific gravity of 1.008. The albumin and sugar were negative. Microscopic examination revealed 18-20 WBC/hpf, an occasional RBC/hpf, and no casts. The urine Sulkowitch was slightly increased. The hematocrit was 34%, and the repeat hematocrit on two other occasions were 39%, and 37% respectively. The sedimentation rate was 40 mm. corrected in one hour. The white count was 6,800 with 2 bands, 78 segs, 16 small lymphs, 3 transitional monocytes, and 1 eosinophil. The blood urea at various periods of hospitalization were 65 mg.%; 63 mg.%; and 68 mg.%. The serum chloride was 98 mEq/liter; $CO_2$ 27 mEq/liter; serum sodium 145 mEq/liter; and serum potassium 4.5 mEq/ liter. The total protein was 6.7 grams percent on the electrophoretic pattern, with 60% albumin, 7% Alpha I globulin, 10% Alpha II globulin, 10% Beta globulin and 14% gamma globulin. They were within the normal range. A sputum for acid-fast smear and culture was negative and no pathogenic organisms grew on routine smear and culture. A fasting blood sugar was 118 mg.%. On December 31, 1962, the alkaline phosphatase was 4 BU; serum calcium 13 mg.% or 6.5 mEq/liter; and serum phosphorus 2.9 mg.% or 1.7 mEq/liter. Repeat studies on January 2, 1963, were as follows: alkaline phosphatase 4.3 BU; calcium 11.4 mg.% or 5.7 mEq/liter; and phosphorus 3.7 mg.% or 2.1 mEq/liter. On January 7, 1963, the alka-

line phosphatase was 6.7 BU; calcium 14.1 mg.% or 7.0 mEq/liter; phosphorus 4.7 mg.% or 2.7 mEq/liter. The blood serology was negative. A PSP test was done with an output in 15 minutes of 150 cc. and 10% excretion; one hour, 170 cc. with 15% excretion; two hours, 100 cc. and 10% excretion; a total of 420 cc. output with 35% total excretion. The first and second strength tuberculin skin tests were negative.

The x-rays of the dorsal lumbar spine showed old ankylosing spondylitis. There was fusion of the epiphyseal joints. There was suggestion of early osteoporotic collapse of the second and third disc of the lumbar area. The chest x-ray showed loculated pleural fluid at the right base. There were multiple calcifications with a constant relationship to the lower pole of the left kidney which was felt due to nephrocalcinosis. He was seen in consultation by the Urologist at this time. It was his feeling that the patient had bilateral pyelonephritis, left nephrolithiasis, and left nephrocalcinosis. He did not find any evidence of urinary tract obstruction, either in the high or lower tract.

A diagnosis of pulmonary infarction from phlebothrombosis in the deep veins of the left leg was made. In view of the fact that he had been taking 50,000 units of vitamin D four times a day for 12 years, it was suspected and confirmed that the patient had vitamin D intoxication.

The vitamin D was therefore stopped and the patient was treated in the usual manner for pulmonary infarction. He showed marked improvement and was discharged home on ambulatory anticoagulants on January 11, 1963.

The patient was admitted again on January 16, 1963, with a recurrent thrombophlebitis in the left leg and left arm in the area of the antecubital fossa. He responded well to his treatment for the thrombophlebitis at this time. The urine specific gravity at this time was 1.008; albumin negative; and sugar negative. The microscopic revealed an occasional WBC/hpf and a rare RBC/hpf, with an occasional epithelial cell. The chemistries at this admission were as follows: urea 44 mg.%; sodium 142 mEq/liter; potassium 4.3 mEq/liter; phosphorus 2.6 mg.%; alkaline phosphatase 4.5 BU; and calcium 6.8 mg.%. A repeat calcium was 9.6 mg.%. The $CO_2$ was 29.0 mEq/liter; chloride 109 mEq/liter. Total protein was 6.9 gm.% with an albumin of 3.6 gm.% and a globulin of 3.3 gm.%. The urine Sulkowitch was 2+.

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On the patient's last office visit, August 5, 1964, he was doing very well. He was being maintained on ambulatory anticoagulants. It was interesting to note at this visit that the patient voluntarily stated that he was not having the mild headaches that he had previously had and he was having no thirst, frequency, hesitancy, or urgency on urination. At this time a routine urine was negative for albumin and sugar, but microscopic revealed 1-5 WBC/hpf and 10-12 RBC/hpf. The serum calcium was 9.2 mg.%; phosphorus 3.7 mg.%; alkaline phosphatase 5 BU. The blood urea was 51 mg.%. Total proteins were 7.3 gm.% with albumin 4.1 gm.% and globulin 3.2 gm.%. A serum potassium was 4.2 mEq/liter.

## Discussion

Vitamin D has been used in the treatment of arthritis, allergy, rickets, psoriasis, acne, trichinosis and hypocalcemic states. Most cases of intoxication have resulted from taking hundreds of times in excess of minimal adult needs over months or years; usually 150,000 units a day or more.[1]

Vitamin D increases calcium absorption

from the gastrointestinal tract and phosphorous excretion in the urine. The sequence of events may be:

(1) Increase calcium absorption
(2) Increase serum calcium level
(3) Decrease parathyroid gland activity
(4) Decrease urinary phosphate excretion because of decreased parathyroid gland activity
(5) Increase serum phosphate level
(6) Supersaturation of blood with respect to calcium phosphate
(7) Precipitation of calcium phosphate in abnormal sites with metastatic calcification (kidneys, bronchioles, alveoli of the lungs, mucus membranes of the stomach, blood vessels, and other tissues.)[2]

Fatal intoxication from vitamin D can be produced without the development of hypercalcemia, pointing to the toxic effects not mediated through its effect on calcium metabolism.[1] If the intoxication with vitamin D is severe, additional manifestations may occur with inspissation of blood as a result of hypercalcemia, acute failure of renal filtration, rapidly rising plasma phosphate and non-protein nitrogen levels, and death from electrolyte imbalance.[2]

If there is a low intake of calcium with hypervitaminosis D, the serum calcium is not high; the serum phosphorous is low, and the blood chemistry changes are similar to hyperparathyroidism. The diagnosis is clear from the excessive intake of vitamin D.[1] Individual susceptability varies; Howard and Myer noted that patients getting twice the dose that their patients had did not get intoxicated from vitamin D. They thought this was due to the variations in intestinal conditions rendering absorption better in some patients or that there may be cellular resistance of an unknown nature to the action of the drug.[3] There are conditions which predispose to developing rapid hypercalcemic states; namely, high intake of calcium,[4, 5] immobilization,[3] and sarcoidosis.[6] The increase calcium absorption in sarcoid is probably due to a hypersensitive response to vitamin D and not an over-dose. A decrease in calcium absorption is seen in renal failure and this is probably due to a decreased responsiveness to vitamin D.[6]

The patient may have one or more of the following symptoms; anorexia; nausea, vomiting, abdominal pain, weight loss, diarrhea, polyuria, nocturia, polydipsia, headaches, drowsiness, weakness, blurred vision, photophobia, hearing impairment, pruritis, depression, stupor, and coma.

On examination there may be abnormal brownish pigmentation of the skin; subnormal temperatures, conjunctival injection and deposition of calcium, hearing loss, mild hypertension in one-fourth of the cases (increased calcium deposition of arteries and accelerated development of atherosclerosis), and band keratitis.

Laboratory results may show the serum calcium elevated; serum phosphorous normal, high, or low; normal alkaline phosphatase; mild anemia; proteinuria; casts; elevated non-protein nitrogen; impaired PSP; fixed specific gravity; Sulkowitch 3 to 4+; and electrocardiographic changes with a short QT interval.

X-rays may show calcification of the periarticular structures. The bones may show osteoporosis but this is probably due to an arthritis rather than vitamin D. Metastatic calcification of other soft tissues as prostate, kidneys, extremities, media of arteries, heart valves, and subcutis choroid plexus are often seen. The intravenous pyelogram shows a decreased ability to excrete the dye.

The diseases to be differentiated from vitamin D intoxication include primary hyperpara-

thyroidism, sarcoidosis, multiple myeloma, primary or metastatic carcinoma of bone, Hodgkins disease, leukemia, Burnette's syndrome, acute osteoporosis of disuse, and idiopathic hypercalcemia of infancy.[7]

The treatment of hypervitaminosis D consists of stopping the vitamin D; avoidance of calcium in the diet; avoidance of exposure to sunlight; and forcing fluids. One may use steroids in cases with central nervous system stupor or coma; with this drug there is an increased urinary and fecal output of calcium.[3] Verner et al had two cases treated with cortisone, and the serum calcium returned to normal in 8 and 13 days without serious complications. Without cortisone the serum calcium may take three months to return to normal, and if renal insufficiency is present it may take 18 months. Cortisone is an important addition in the treatment of the critically ill with this disease. It is useful therapeutically and may be of help diagnostically as a trial in distinguishing hypercalcemia of hyperparathyroidism; cortisone does not affect calcium level of hyperparathyroidism, whereas in hypervitaminosis D and sarcoid the calcium level is greatly reduced in 10 days after 150-200 mgm a day. While on cortisone a careful control of fluid balance is necessary. The prompt return of serum calcium to normal would favor a more rapid decrease in blood urea.[7]

## Case

This 41-year-old man without a prescription had been able to get vitamin D in large doses for 12 years. At no time was he warned of the possible toxic effects of the drug. The vitamin D was apparently given for arthritis. He had had three previous hospital admissions, two for complications with bladder calculi; vitamin D intoxication was not suspected. He had headaches, thirst, frequency, hesitancy, and urgency of urination. The laboratory confirmed the metabolic abnormalities of calcium and showed impairment of renal function. The x-rays showed nephrocalcinosis. After withdrawal of the vitamin D, the symptoms improved and the blood calcium metabolic levels returned towards normal in 18 months. He was not given cortisone therapy because he did not seem critically ill as far as his complications from vitamin D were concerned.

## Summary

*A case is reported of a 41-year-old man who took 200,000 units of vitamin D for 12 years to help his arthritis, only to find out it had led to serious complications of hypervitaminosis D. The patient was showing continued improvement at the time of his last visit 18 months after discontinuing vitamin D.*

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Otro aspecto a considerar es la insuficiencia renal que padecían los enfermos presentados. La insuficiencia renal es una complicación importante del mieloma múltiple [17] y es atribuida generalmente a los efectos de la proteinuria de Bence-Jones sobre la función tubular [16]. Se conocen, además, otros factores que pueden producirla, como la hipercalcemia, depósitos de ácido úrico, infiltración de células del mieloma, amiloidosis, pielonefritis, anemia y viscosidad aumentada de la sangre. Raramente la insuficiencia renal es debida a depósitos intraglomerulares de la globulina sérica anormal [17, 18].

De los factores arriba enumerados solamente algunos pueden haber causado la insuficiencia renal en los casos presentados. En el caso número 2 hay que señalar la amiloidosis, depósitos intratubulares de proteínas, pielonefritis y proteinuria de Bence-Jones. La proteinuria de Bence-Jones, como ocurre en este enfermo, a veces no muestra la precipitación característica entre 40 y 70° de temperatura y su redisolución a los 100°. Se debe fundamentalmente a que el pH y la concentración de proteínas y sales no son los adecuados, siendo la electroforesis el método más útil para detectarla. En el caso número 1 solamente se conocen como factores causantes de la insuficiencia renal, además de la amiloidosis y depósitos intratubulares proteicos, la hipercalcemia.

La insuficiencia renal empobrece el pronóstico del mieloma, sobre todo si se favorecen las condiciones de precipitación intratubular de proteínas con orinas ácidas y restricción de líquidos. De ahí que una mayor ingesta de líquidos y alcalinización de la orina son medidas que deben incluirse en el tratamiento del mieloma para evitar el empeoramiento de la insuficiencia renal.


## Resumen

Se describen dos casos de mieloma múltiple con proteína de movilidad electroforética alfa$_2$ y [illegible]ación renal secundaria, uno de ellos asociado a amiloidosis y otro exteriorizado como una artritis reumatoide. Se comenta los posibles mecanismos de la insuficiencia renal y algunos aspectos de la inmunología del mieloma.


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# INTOXICACION POR VITAMINA D COMO CAUSA DE POLIURIA


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## Introducción

Desde el año 1928, a través de las publicaciones de Hess y Lewis [1], conocemos los efectos desfavorables que puede producir la vitamina D a grandes dosis o la administración de cantidades moderadas a personas que padecen hipersensibilidad a la misma.

Después y de forma progresiva ha ido proliferando el número de comunicaciones comentando aspectos parciales o generales de esta situación; por lo que actualmente está bien delimitado el síndrome clínico y bioquímico, así como la terapéutica que debe establecerse.

En nuestro país, suponemos que la intoxicación por vitamina D es relativamente frecuente, basándonos en la experiencia de cuatro casos que hemos tenido ocasión de estudiar en la Fundación a lo largo de un curso. También en el hecho de que existen multitud de preparados de vitamina D aislados o en combinación y alimentos enriquecidos, teniendo a todos ellos fácil acceso cualquier persona; y, finalmente, consideramos que la dieta rica en Ca y el clima con muchos días de sol en la mayor parte de nuestra geografía, pueden ser coadyuvantes en alguna medida.

En el presente trabajo nos referiremos solamente a dos casos seguidos más directamente en nuestro Departamento.

*Caso núm. 1.*— F. T. S., veinte meses. Nació de embarazo y parto normal. A los diez meses advirtió su familia que la niña bebía mucha agua a la vez que sus diuresis eran abundantes con orinas claras. El apetito había disminuido paralelamente, pero no existían otros signos o síntomas dignos de mención.

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Aportaba unos análisis de orina con densidades que oscilaban entre 1.001 y 1.009, y que no se modificaban con la inyección de cinco unidades de tanato de pitresina.

A la exploración, la niña tenía un desarrollo adecuado para su edad. Buena coloración de piel y mucosas. Bien hidratada. Exploración cardiopulmonar normal.

T. A., 9,5/6,5. Abdomen blando, no se palpa el hígado, el bazo ni los riñones. No edemas. No se aprecian adenopatías.

Los primeros análisis nos demuestran muy discreta anemia. La V. de S. es normal para su edad. Leucocitos y fórmula normales. Se comprueba en determinaciones seriadas densidades urinarias bajas.

Inicialmente tomamos como punto de partida el diagnóstico de diabetes insípida. Orientando las siguientes exploraciones en la forma que a continuación exponemos, tratando de dilucidar la causa de su incapacidad para concentrar la orina.

Con la prueba de la sed y la inyección de dosis saturantes de pitresina, que no modificaron las diuresis ni la densidad, descartamos todos los cuadros de diabetes insípida de origen central. Después, pasando revista a todos los procesos que cursan con poliuria de origen renal, pudimos descartar unos y otros con los datos clínicos y bioquímicos de que disponíamos, hasta llegar al grupo de las hipercalcemias. Realizadas varias determinaciones de calcio en sangre obtuvimos cifras de más de 11 mg. por 100. Su cuadro clínico no correspondía ni a hiperparatiroidismo ni a sarcoidosis ni tampoco a ningún proceso maligno de los que cursan con hipercalcemia. La constitución de la enferma, su desarrollo y nivel mental adecuados y los datos bioquímicos tampoco sugerían el diagnóstico de hipercalcemia idiopática. Por tanto, quedaba como única posibilidad para encajar su cuadro, la intoxicación por vitamina D, que la niña había recibido en dosis tóxicas (20.000 unidades diarias durante un mes), según comprobamos en un segundo interrogatorio dirigido.

Concretado este diagnóstico intentamos realizar un balance del calcio que fue imposible por la dificultad que entrañaba la recogida completa de heces y orina en una niña de tan corta edad. Pero en determinaciones aisladas se obtuvieron calciurias de más de 200 mg. en 24 horas. También se practicó una biopsia renal, cuyo estudio demostró depósitos de calcio en el interior de algunos túbulos que en ocasiones se continuaban con el intersticio. (figura 1).

Sometida a un régimen pobre en calcio y evitando todo aporte de preparados de vitamina D, se instituyó un tratamiento con 30 mg. de prednisona al día durante diez días.

Con sólo este tiempo de medicación asistimos a una mejoría clínica evidente. Aumentó el apetito, desapareciendo la poliuria y la polidipsia. El Ca en sangre disminuyó hasta 9 mg., así como las calciurias por veinticuatro horas que se redujeron a unos 60 mg. La densidad de la orina ascendió espontáneamente hasta 1.016, llegando hasta 1.025 con la inyección de 5 unidades de tanato de pitresina (cuadro núm. I).

CUADRO I

*Modificaciones que se observaron en la enferma F. T. S., después del tratamiento con prednisona. En condiciones basales se realizó una prueba de la sed y dos inyecciones de pitresina 5 + 5 U., sin que se modificaran la diuresis ni la densidad. Después del tratamiento, la densidad ascendió espontáneamente a 1.016, llegando a 1.027 con la prueba de la sed y la inyección de 5 U. de pitresina.*

| | Basales | Después del tratamiento con prednisona |
|---|---|---|
| Diuresis ..... | 800-1.500 | 400-500 |
| Densidad ..... | 1.003-1.006 | 1.016-1.027 |
| Calcio en sangre ..... | 11,5-12 mg. % | 9,6-10 mg. % |
| Fósforo en sangre ... | 4,4-4,8 mg. % | 3,1-3,1 mg. % |

*Caso núm. 2.* — B. C. C., diecinueve meses. Nació a término, después de un embarazo normal, pesando 3 kilogramos. En el parto fue necesario utilizar ventosa. Tenía cierto grado de cianosis en relación con varias vueltas de cordón. Se le administró oxígeno y en seguida

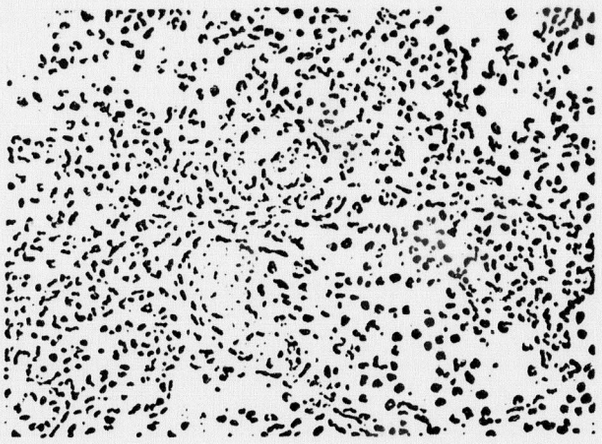

Fig. 1.—F. T. S. Veinte meses. Biopsia renal percutánea. Intersticio renal infiltrado fundamentalmente por linfocitos. Cilindros grumosos en los túbulos y depósitos de calcio. HE. × 160.

se recuperó. Durante dos meses se alimentó sólo con leche materna, ganando peso y desarrollándose normalmente. A los siete meses pesaba 8 kilogramos.

Insidiosamente el apetito disminuyó, apareciendo sed intensa y vómitos ocasionales. Recibió frecuentemente vitaminas, entre ellas vitamina D y calcio, sin poder precisar dosis ni tiempo. Orina mucha cantidad noche y día.

No refieren casos semejantes entre sus familiares.

A la exploración: La niña tiene un desarrollo inferior al que le corresponde. Buena coloración de piel y mu-

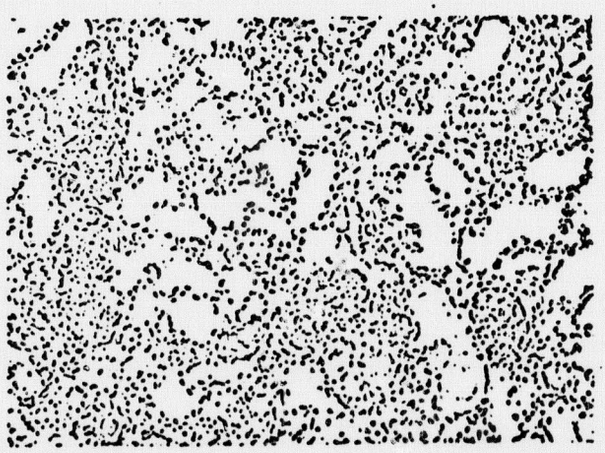

Fig. 2.—B. C. C. Diecinueve meses. Biopsia renal percutánea. Nefrocalcinosis con reacción intersticial; dilatación tubular. Ovillo glomerular normal. HE. × 90.

cosas. Dentición normal para su edad. Exploración cardiopulmonar normal. T. A., 11/7. Abdomen, blando, no se palpa el hígado, el bazo ni los riñones. No edemas.

Datos complementarios: Sangre, anemia muy discreta. Leucocitosis de 18.000 con 9 cayados, 4 eosinófilos, Na. 134, K. 4,7, Cl. 87, R. A. 21 (mEq/l.), pH. 7,52, uremia 0,26 gm/l. Proteinograma sin alteraciones. El Ca. aparecía elevado 14,6 mg. por 100; P., 2,1; F. A., 17,6. Colesterina, normal para su edad: 189 mg. por 100.

Orina: discretas alteraciones en el sedimento, con indicios de proteinuria, densidad de 1.005. Siembra de ori-

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na, negativa. El estudio seriado nos demuestra una poliuria de unos 1.000 c. c. por 24/h., con densidades que oscilan entre 1.001 y 1.008 y no se modifican con la inyección de dosis saturantes de pitresina.

Las eliminaciones diarias de Na. y K. son adecuadas a la ingesta.

El filtrado glomerular medido por el aclaramiento de creatinina está descendido a unos 6 c. c./min., correspondiéndole unos 30 c. c./min.

El estudio radiológico no demuestra calcificaciones renales. La base del cráneo está normalmente calcificada, las impresiones digitales sin aumentar y suturas normales. El extremo de las epifisis está hipercalcificado. La edad ósea radiológica es algo menor que la edad real.

Se practicó una biopsia renal, en la que solo aparecen

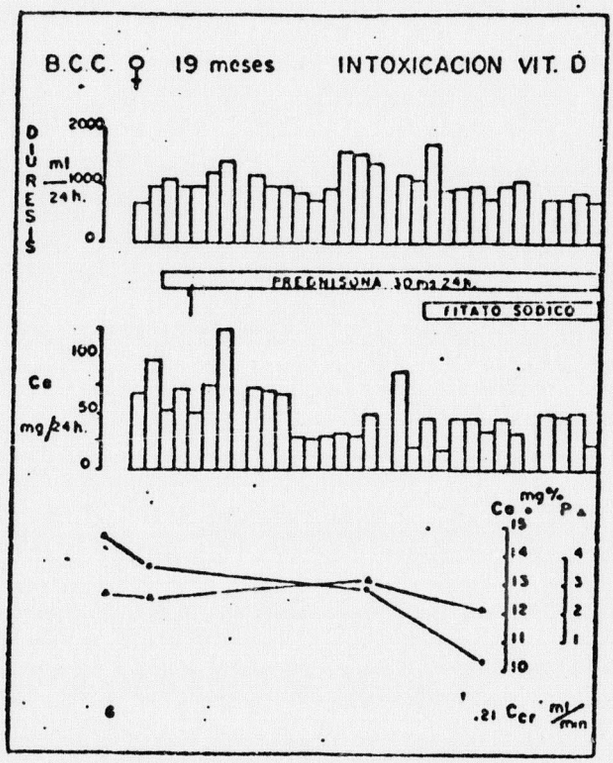


Fig. 3.—B. C. C. Evolución de la diuresis, calciurias, cifras plasmáticas de Ca y P y filtrado glomerular en relación con el tratamiento con esteroides y fitato.

pequeños depósitos de Ca en algunos túbulos e intersticio con cierto grado de reacción inflamatoria intersticial (fig. 2).

Con estos datos nos planteamos el diagnóstico diferencial entre la hipercalcemia idiopática y la intoxicación por vitamina D, descartando las demás causas de hipercalcemia por razones clínicas.

En contra de la intoxicación por vitamina D teníamos la falta de evidencia de administración de vitamina D a grandes dosis, la ausencia de alcalosis metabólica (la enferma tenía 7,52 de pH., pero con R. A. de 21), coincidiendo siempre con hiperventilación en el momento de la extracción, ya que la niña lloraba, y la falta de alteraciones óseas específicas.

Sin embargo, su cuadro tampoco encajaba en el de hipercalcemia idiopática. Faltaban las alteraciones somáticas que la caracterizan (epicanto, frente alta, calcificación de la base del cráneo, etc.). Aparte de algún dato analítico que tiene cierto valor, como es la colesterina en sangre, que suele estar elevada y en nuestra enferma era normal.

Por todo ello nos inclinamos por el primer diagnóstico, apoyándonos en la evolución y respuesta al tratamiento que fue más en consonancia con intoxicación por vitamina D.

Durante su estancia en la Clínica, y después de tomar las medidas de orden general, se decidió un tratamiento con esteroides, 30 mg./día de prednisona. Con ello, y de forma progresiva, la enferma mejoró clínicamente, se hizo más sociable, se alimentó mejor y ganó peso. La cifra de calcio descendió, aumentando el filtrado glomerular, como muestra la figura 3.

## Comentarios

Al presentar estos dos enfermos nos proponemos llamar la atención sobre la frecuencia con que casos similares pueden darse, por las razones que mencionábamos en la introducción.

Al mismo tiempo queremos resaltar los aspectos interesantes de diagnóstico, evolución y tratamiento, haciendo hincapié en la extraordinaria importancia que tiene el planear de forma ordenada un diagnóstico diferencial completo, pues los enfermos casi nunca nos dirán que tomaron vitamina D, sino sólo sus síntomas, más o menos orientadores. Pero es más, aun conociendo el antecedente de administración de vitamina D puede ser difícil saber las dosis exactas.

Los síntomas de la intoxicación por vitamina D, están condicionados por la hipercalcemia que produce a través de los siguientes mecanismos:

1. Aumenta la resorción de Ca en el tubo digestivo y secundariamente de P.
2. Aumenta la resorción de fosfatos por los túbulos renales, con lo que disminuye su eliminación y aumentan sus niveles en sangre. En ausencia de parathormona aumenta la eliminación de P.
3. Moviliza el calcio de los huesos cuando el calcio de la dieta no es suficiente.
4. Regula el equilibrio entre el calcio de los huesos y el de la sangre, acción mediatizada por las glándulas paratiroideas.

Las necesidades de vitamina D para un niño son de unas 300 unidades/día.

## Diagnóstico diferencial

Estos enfermos acuden al médico aquejando polidipsia, poliuria y muchas veces con varios análisis de orina, en los que persiste una densidad baja.

El primer diagnóstico sindrómico que deberá establecerse es por tanto el de diabetes insípida.

Repasando las publicaciones de Warbener [5] sobre este tema encontramos un gran número de procesos que cursan con esta alteración siendo fácilmente desglosables en dos grandes grupos:

A) Diabetes insípida de origen central.
B) Diabetes insípida nefrogénica.

La prueba diagnóstica de fácil realización que nos determinará en qué grupo está incluido un enfermo con poliuria, es la inyección de dosis saturante de pitresina. Si el volumen y la densidad no se modifica aceptaremos que existe una

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incapacidad del riñón para responder a la A. D. H., tratando posteriormente de buscar el porqué de esta falta de respuesta.

En este apartado, incluiremos como causas posibles las siguientes:

a) Diabetes insípida nefrogénica esencial.
b) Síndromes tubulares complejos (Fanconi, cistinosis).
c) Depleción de K.
d) Oclusión parcial de arteria renal.
e) Drepanocitosis.
f) Diuresis osmóticas.
g) Pielonefritis.
h) Hipercalcemias.

El primer diagnóstico siempre lo será de exclusión por no conocer la causa y no tener unas alteraciones típicas que lo confirmen. Se suele dar en varones. En ocasiones existen antecedentes familiares. No responden ni a la deprivación de líquidos ni a la inyección de tanato de pitresina, aunque se ha comprobado que si con reducción de líquidos la pérdida del peso corporal llega a un 5 por 100, puede ascender la densidad sin que sepamos las razones.

En los cuadros tubulares más complejos del tipo del Fanconi, cistinosis, etc., encontraríamos a través de las determinaciones pertinentes otras manifestaciones de alteración tubular como son glucosuria, fosfaturia, aminoaciduria, etc.

En la depleción de K obtendríamos una cifra baja de este catión en sangre, buscando posteriormente las causas de su depleción: vómitos, diarreas, diuréticos, pérdidas renales por otras causas.

La drepanocitosis es una enfermedad que no se da en nuestro medio y que citamos como curiosidad.

La diuresis osmótica será fácil de descubrir por el antecedente de administración de alguna de las sustancias que la producen o mediante el diagnóstico de determinadas situaciones clínicas en que aparecen.

La pielonefritis es una enfermedad cuya clínica es bien conocida, pudiendo en último caso practicar una biopsia renal con la que obtendríamos un diagnóstico de seguridad.

Por último, tenemos el grupo de las hipercalcemias en el que están incluidas diversas enfermedades que pueden cursar con poliuria, y que a continuación enunciamos:

Sarcoidosis.
Hiperparatiroidismo.
Diversos tumores con o sin metástasis óseas. Mieloma, linfoma, leucemias, Hodgkin.
Hipercalcemia idiopática.
Síndrome de leche alcalinos.
Intoxicación por vitamina D.

Para hacer el diagnóstico diferencial de este grupo de enfermedades creemos muy conveniente dividirlas en dos grandes grupos. Aquellas cuya sintomatología no sólo depende de la hipercalcemia y cuyo diagnóstico está hecho muchas veces antes de que aparezca este signo y entre las que incluimos: sarcoidosis, hiperparatiroidismo, tumores, mieloma, linfomas, leucemia, Hodgkin; y un segundo grupo cuya sintomatología fundamental está producida por la hipercalcemia, que comprende el resto; si bien en los casos de síndrome de leche y alcalinos puede perdurar la sintomatología del ulcus.

En el primer grupo están incluidos una serie de cuadros que conservan unas características clínicas y bioquímicas y anatomopatológicas que difícilmente nos llevarán a confusión entre ellas.

El síndrome de leche y alcalinos es de fácil diagnóstico si lo planteamos y, finalmente, nos queda la hipercalcemia idiopática y la intoxicación por vitamina D, cuya diferenciación puede ser difícil.

La hipercalcemia idiopática es una enfermedad que habrá que aceptar sólo cuando hayamos descartado el resto de los procesos que cursan con hipercalcemia. Son niños desnutridos con historia de vómitos de repetición, estreñimiento, polidipsia y poliuria. Somáticamente conservan algunas peculiaridades, como son el epicanto, frente despejada, arco nasal hundido, mandíbula pequeña. Radiográficamente podemos descubrir una esclerosis de los huesos de la base del cráneo. Bioquímicamente se ha descrito la existencia de una cifra de colesterina elevada y también acidosis hiperclorémica.

La intoxicación por vitamina D es un diagnóstico a aceptar cuando existe el antecedente claro de administración de dosis tóxicas de dicha vitamina. Sin embargo, cuando existen dudas sobre la cantidad administrada puede ser difícil concretar este diagnóstico. Clínicamente, como ya hemos señalado, tienen un cuadro íntimamente ligado a la hipercalcemia. Radiológicamente se ha descrito aumento de densidad de los extremos de crecimiento de los huesos con rarefacción en eje de los mismos; también se pueden encontrar densas líneas metafisarias. Bioquímicamente puede ser un dato importante la existencia de una alcalosis metabólica.

Una prueba retrospectiva que puede ser útil en el diagnóstico diferencial de una hipercalcemia es la administración de esteroides. Con este tratamiento podemos disminuir la calcemia en aquellos procesos en los que el mecanismo de la hipercalcemia reside en un aumento de la resorción del calcio a nivel intestinal como son la sarcoidosis, la hipercalcemia idiopática y la intoxicación por vitamina D. El resto de los procesos cuya hipercalcemia parece estar más en relación con la liberación del calcio óseo no responderían a esta terapéutica.

En el siguiente cuadro II resumimos, finalmente, las alteraciones bioquímicas más características de algunos cuadros que cursan con hipercalcemia [12].

## Evolución

Suele ser favorable si no ha trascurrido mucho tiempo y no existen grandes depósitos cálcicos viscerales.

CUADRO II

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*Resumen del diagnóstico diferencial de los datos bioquímicos más importantes de algunos procesos que cursan con hipercalcemia.*

| | Calcemia | Calciuria | Fosforemia | Equilibrio ácido-base | Fosfatasas |
|---|---|---|---|---|---|
| Hiperparatiroidismo | + | + | — | Normal. | + |
| Intoxicación Vit. D | + | + | + | Alcalosis metabólica. | |
| Sarcoidosis | + | + | + | Alcalosis metabólica. | |
| Síndrome de Burnett | + | + | | Alcalosis metabólica. | |
| Neoplasias | + | + | + | Alcalosis metabólica. | + |
| Síndromes paraneoplásicos | + | + | — | Normal. | |
| Hipercalcemia idiopática | + | + | | A veces acidosis hiperclorémica. | |

## Tratamiento

Comprende cuatro apartados:

1.º Retirar toda medicación de vitamina D y calcio. Instaurando una dieta con poco calcio.

2.º Medicación sintomática.

3.º Corregir el déficit de agua y sodio y potasio si existiera.

4.º Tratamiento específico con esteroides.

En relación con el primero y segundo apartado no parece necesario insistir más ni extendernos en más comentarios, pues nos parecen obvios.

El tercer apartado es importante, pues la hipercalcemia produce, con la poliuria, pérdidas de agua, sodio y potasio con disminución del volumen circulante y posible insuficiencia renal por este mecanismo.

El tratamiento con esteroides tiene una base fisiopatológica [9], ya que existen observaciones de enfermos de Cushing y otros tratados con dosis altas de esteroides que desarrollaban hipocalcemias, a través de una disminución de la absorción de Ca a nivel intestinal. Por este motivo se ensayó esta terapéutica en distintos procesos con hipercalcemia, siendo de utilidad en las situaciones concretas ya mencionadas.

La dosis y duración del tratamiento variarán en cada caso, pero es fundamental insistir todo el tiempo que sea preciso hasta que aparezca una mejoría clínica y se corrijan las alteraciones bioquímicas.

## Resumen

Se presentan dos casos de intoxicación por vitamina D, en dos niños de corta edad; comentando los aspectos de historia clínica, exploración física, datos complementarios, diagnóstico, evolución y tratamiento.

Señalamos la relativa frecuencia de este proceso en España y las posibles causas; pasando revista a los mecanismos de producción de hipercalcemia por la vitamina D y necesidades de la misma. A continuación se desarrolla el diagnóstico diferencial del síndrome de poliuria. Comentando finalmente la evolución y el tratamiento desde el punto de vista general sintomático y específico con esteroides.

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# Nephrotoxic Effect of Vitamin D Therapy in Vitamin D Refractory Rickets

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Hypophosphataemic vitamin D refractory rickets is a rare disease which may be inherited as a sex-linked dominant (Winters *et al.*, 1958), and is characterized by the development of the stigmata of rickets in the first year of life. There is often considerable delay before the correct diagnosis is made, and by then there may be some retardation of growth (Fraser and Salter, 1958). The rickets can be healed by very large doses of vitamin D (Albright, Butler, and Bloomberg, 1937), but the margin between the therapeutic dose and the toxic dose of vitamin D is small (Fraser and Salter, 1958). Vitamin D in toxic doses causes hypercalcaemia leading to nephrocalcinosis (Parfitt, 1964; David, Verner, and Engel, 1962).

We have recently studied 4 children with vitamin D refractory rickets to assess the likelihood of development of toxic effects from carefully monitored long-term treatment with vitamin D.

## Material and Methods

Four children with hypophosphataemic vitamin D refractory rickets are the subject of this report. These children had developed rickets despite an adequate intake of vitamin D, and all had a low serum phosphate, normal serum calcium, and raised serum alkaline phosphatase at the time of diagnosis. Initial urinary studies showed excessive phosphate loss, normal amino acid excretion, and no reducing substances. They were treated with vitamin D, the dose being adjusted according to the values of the serum calcium and the 24-hour urinary calcium which were measured monthly; the results are summarized in Tables I and II. The serum phosphorus, alkaline phosphatase, latterly urea, and urinary phosphorus were also measured monthly, but the results are not reported here. Three of the children also received buffered isotonic sodium phosphate solution equivalent to 1·3 g. phosphorus daily. The rachitic deformities have improved and growth has been in the normal range. No child has had a urinary tract infection.

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## Case Histories

**Case 1.** This girl was referred to hospital in 1962 at the age of 2 years with bowed legs. She had been fed on Cow and Gate milk from the age of 3 weeks, had started solids at 10 weeks of age, and had been given additional vitamins from the age of 1 month. On examination the wrists and ankles were swollen as were the costochondral junctions. There was 1·25 cm. between the knees with the malleoli touching. Her height was between the 3rd and 10th centiles for her age. An *x*-ray of the wrist showed healing rickets. The serum calcium was 10·0 mg./100 ml., phosphorus 2·5 mg./100 ml., urea 17 mg./100 ml., and alkaline phosphatase 27 KA units. She was treated with vitamin D3, and for most of the time has received 1 mg. daily. Six months after treatment was started she developed symptoms of hypercalcaemia, with a raised serum calcium, and vitamin D3 therapy was stopped for 2 months. Since then she has had two brief episodes of hypercalcaemia during which therapy has been stopped. Her rachitic deformities initially resolved, but recently she developed a mild genu valgum which was corrected with night splints. Her height is now on the 25th centile for her age (Fig. 1), and a recent *x*-ray of the wrist shows that the rickets has healed.

**Case 2.** When this girl was admitted to hospital in 1960 at the age of 2 years because she was not walking, she was found to have slight bowing of the legs, swelling of the wrists and ankles, and slight swelling of the costochondral junctions. She had received Cow and Gate milk and daily cod liver oil from the age of 1 month. Her height was on the 3rd centile for her age, and an *x*-ray of the wrist showed active rickets. The serum calcium was 8·9 mg./100 ml., phosphorus 2·4 mg./100 ml., urea 19 mg./100 ml., and alkaline phosphatase 66 KA units. She was treated with vitamin D3 and isotonic buffered sodium phosphate solution. Despite full co-operation, control proved difficult and she subsequently developed hypercalcaemia on 5 occasions during which vitamin D3 therapy was stopped. The phosphate solution was discontinued between September 1962 and April 1966. In 1965 cruciate craniectomy was necessary for relief of raised intracranial pressure due to complete craniosynostosis. Her height is now

TABLE I

*Number of Monthly Measurements of Serum Calcium*

| Case No. | Duration of Treatment (yr.) | Serum Calcium (mg./100 ml.) | | | | Total No. of Measurements |
|---|---|---|---|---|---|---|
| | | <10 | 10–10·9 | 11–11·9 | >12 | |
| 1 | 5 | 36 | 18 | 1 | 3 | 58 |
| 2 | 7½ | 25 | 35 | 21 | 9 | 90 |
| 3 | 8 | 36 | 40 | 12 | 3 | 91 |
| 4 | 15½ | 65 | 80 | 21 | 7 | 173 |

TABLE II

*Number of Monthly Measurements of 24-hour Urinary Calcium Excretion*

| Case No. | Duration of Treatment (yr.) | Urinary Calcium (mg./24 hr.) | | | Total No. of Measurements |
|---|---|---|---|---|---|
| | | <100 | 100–199 | >200 | |
| 1 | 5 | 12 | 28 | 5 | 45 |
| 2 | 7½ | 65 | 12 | 6 | 83 |
| 4 | 15½ | 20 | 34 | 42 | 96 |

*Note:* Urine collections were unreliable in Case 3.

on the 25th centile for her age (Fig. 1) and the rickets is still slightly active radiographically, though she now has no skeletal deformities. She has received between 0·75 and 2 mg. of vitamin D3 daily for most of the duration of treatment.

**Case 3.** This boy was referred to hospital in 1959 at the age of 9 years, with severe knock-knee, which had been first noticed at the age of 3 years. Mixed feeds had been started at the age of 6 months and he had been given cod liver oil intermittently from that age. He was found to have advanced knock-knee with 14·6 cm. of intermalleolar separation, and slight swelling of the wrists. His height was below the 3rd centile for his age and an *x*-ray of the wrist showed active rickets. The serum calcium was 8·7 mg./100 ml., phosphorus 2·1 mg./100 ml., urea 32 mg./100 ml., and alkaline phosphatase 39 KA units. His father also had bowed legs and the serum phosphorus was 2·9 mg./100 ml. He was treated with vitamin D3 and isotonic buffered sodium phosphate solution. He has remained well, and his deformities have slowly resolved. His height is now on the 10th centile for his age (Fig. 2). A recent *x*-ray of the wrist showed that the rickets was still active. He has had 4 short periods of hypercalcaemia during which vitamin D3 was discontinued. His dose of vitamin D3 has varied between 2 and 6 mg. a day for most of the time since diagnosis.

**Case 4.** This girl was noticed to have bowed legs at the age of 20 months and was admitted to hospital in 1952 at the age of 4 years. Her general health had been good and she had had cod liver oil daily from the age of 4 months. She had marked bowing of the legs, with 7·6 cm. separation between the knees, and the costochondral junctions were slightly enlarged. Her height was below the 3rd centile for her age. An *x*-ray of the knees showed late, slightly active rickets. The serum calcium was 11·4 mg./100 ml. phosphorus 2·2 mg./100 ml., urea 25 mg./100 ml., and alkaline phosphatase 55·8 KA units. She was treated initially with calciferol, but in 1956 treatment was changed to vitamin D3 and from 1959 onwards she was given isotonic buffered sodium phosphate solution in addition. In 1954 she had a bilateral osteotomy of the tibiae. Her deformities have persisted, though improved by the osteotomy, and her height has continued on the 3rd centile (Fig. 1). *X*-rays of the wrist show that the rickets has not been active for the past 8 years. Her dose of vitamin D3 has varied between 3 and 5 mg. daily since 1956, and she has had one prolonged, and three short, periods of hypercalcaemia.

## Methods

The patients were admitted to hospital in 1968 for investigation of renal function. The urine was tested for protein by Albustix test tapes (Ames) and for reducing substances by Clinitest tablets (Ames). Creatinine clearance was measured twice during two consecutive 3-hour collections of urine with one blood sample taken between the collections. The serum and urine creatinine were measured on the Auto-Analyser using a modification of the standard Technicon method. The duplicate estimates of creatinine clearance agreed showed good agreement. The result is given as the mean of the two values corrected to a surface area of 1·73 m². The extent to which the urine could be concentrated during a period of fluid deprivation was measured by weighing successive samples of urine in a specific

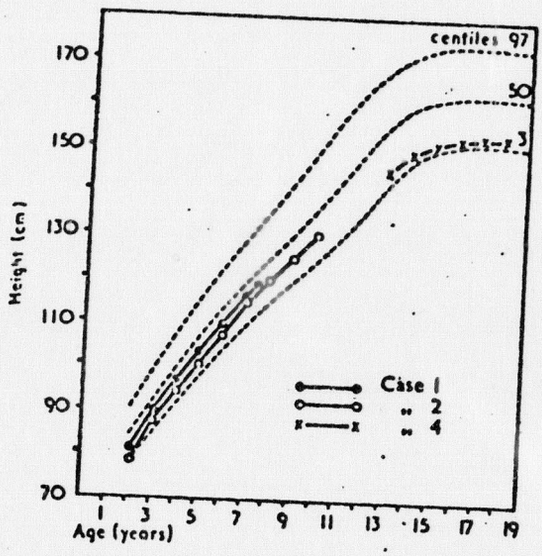


FIG. 1.—*Growth chart (Tanner, Whitehouse, and Takaishi, 1966) showing height in Case 1* o—o—●, *Case 2* o—o—o *and Case 4* x—x—x.

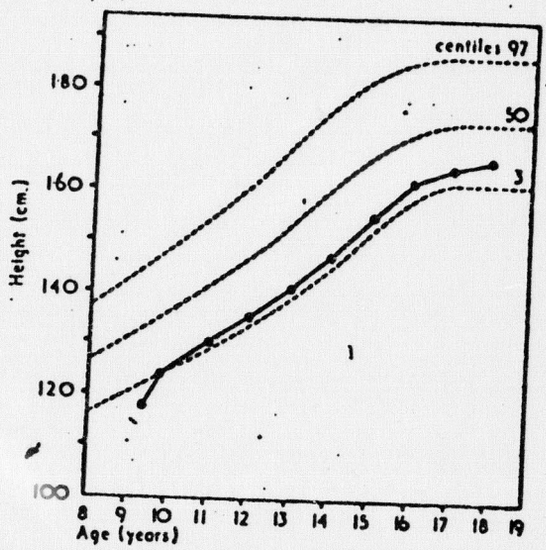


FIG. 2.—*Growth chart (Tanner et al., 1966) showing height in Case 3* o—●—●.

gravity bottle and recording the time taken to achieve a specific gravity of 1022 or greater. The ability to excrete an acid load was assessed by performing the ammonium chloride test in the following manner. After collecting urine for about 2 hours a dose of ammonium chloride $\left(\frac{5 \text{ g.} \times \text{surface area (sq. m.)}}{1{\cdot}73}\right)$ was given. Three further consecutive 2-hour urine specimens were collected, each accurately timed and immediately cooled to −20 °C. to await analysis. Urinary ammonia was estimated by applying directly to urine the phenol-hypochlorite method, as described by Horn and Squire (1966). Titratable acidity was estimated using the method of Henderson and Palmer, as described by Peters and Van Slyke (1931), in which the urine is titrated to *p*H 7·4 using 0·1 N NaOH, with phenol red as indicator. The results were expressed as micro-equivalents of ammonia and titratable acid excreted per minute, both corrected to a surface area of 1·73 sq. m. The *p*H of the urine was measured with narrow range *p*H indicator papers. After intravenous pyelography, percutaneous renal biopsy was performed using local anaesthesia according to the method described by White (1963). The specimens were fixed in 10% formol saline, sectioned at 2–3 μ, and stained by Von Kossa's method and with haematoxylin and eosin, PAS, and Weigert's elastic van Gieson stain.

## Results

The intravenous pyelogram was normal in the 4 children, and their urines did not contain protein or reducing substances. The results of the remaining investigations are shown in Table III. Creatinine clearance was normal in 3 cases, but reduced to half in Case 2. All 4 cases were able to concentrate urine satisfactorily. The ammonium chloride load test was abnormal in all. Case 2 was unable to excrete urine with a *p*H below 5·8, ammonia excretion was impaired in all, and the urinary titratable acidity was just below normal in Cases 1 and 4.

Renal biopsy was performed in Cases 1, 2, and 3. The specimens from Case 1 consisted of cortex and medulla and contained 17 glomeruli: these showed slightly increased cellularity and slight increase of centrilobular fibrillary material. Calcification was present in several areas within the medulla related to the tubules (Fig. 3). The specimens from Case 2 consisted of cortex only and contained 37 glomeruli. Almost half the glomeruli were sclerosed, and several others were partially sclerosed. In several glomeruli there was a moderate amount of endothelial cell proliferation, with loss of capillary spaces, and there were many deposits of calcific material in the interstitial tissues, but none in the tubules or glomeruli (Fig. 4). The specimens from Case 3 consisted of cortex and medulla, and contained 18 glomeruli, of which 2 were sclerosed and the remainder normal. Two small deposits of calcium were present related to

TABLE III

*Results of Investigation of Renal Function in 4 Patients with Vitamin D Refractory Rickets*

| Case No. | Creatinine Clearance (ml./min. per 1·73 m.²) | Urine Concentration Test SG of Urine | Ammonium Chloride Load Test | | |
|---|---|---|---|---|---|
| | | | pH of Urine | Titratable Acidity (μEq./min.) | Ammonia (μEq./min.) |
| 1 | 96 | 1026 in 17½ hr. | 5·0 | 23·5 | 14·5 |
| 2 | 52 | 1034 in 18 hr. | 5·8 | 35·9 | 9·8 |
| 3 | 123 | 1027 in 16½ hr. | 5·2 | 33 | 14·4 |
| 4 | 180 | 1025 in 16½ hr. | 5·2 | 21 | 28·6 |
| Normal | 85–146* | 1022† in 24 hr. | 5·3 † or less | 24–51‡ | 33–75‡ |

* Winberg (1959). † Fishberg (1954). ‡ Wrong and Davis (1959); Matsuda *et al.* (1968).

the tubules, one in the cortex and one in the medulla (Fig. 5).

## Discussion

These 4 children were considered to be suffering from vitamin D refractory rickets for which no cause could be found. None had evidence of malabsorption or of renal failure, and in no case was there an abnormal excretion of amino acids or reducing substances in the urine. They were treated with large doses of vitamin D, and in addition buffered isotonic sodium phosphate solution was given to 3 of them, as recommended by West *et al.* (1964). The dose of vitamin D3 was adjusted so that as far as possible the monthly serum calcium level was maintained below 11 mg./100 ml. in the early years and below 10 mg./100 ml. during the past 3 years. The control with vitamin D therapy has been best in Case 1, with only 7% of the monthly serum calcium measurements over 11 mg./100 ml. Control in Cases 3 and 4 has been moderately good, with approximately 15% of the monthly serum calcium measurement over 11 mg./100 ml. Despite full co-operation and careful monitoring, control has been poor in Case 2 who has suffered from 5 periods of hypercalcaemia, the serum calcium having been above 11 mg./100 ml. for one-third of her period of therapy.

There was no correlation between the 24-hour urinary calcium excretion and the subsequent development of renal damage; Case 2 has had a urinary calcium excretion over 100 mg. in 24 hours for only 20% of the duration of her therapy, and has been found to have severe renal damage, whereas Case 1 has had a urinary calcium excretion over 100 mg. in 24 hours for approximately 70% of the duration of therapy and has only a little calcium deposited in the kidney. This lack of correlation may be due to Case 2 having a low glomerular filtration rate impairing calcium excretion, or to the wide range of normal 24-hour urinary calcium excretion (Knapp, 1947), which varies with calcium intake and body weight.

Growth in each case has been within the normal range after an initial period of acceleration in 3 patients. In Case 4 it has only been on the 3rd centile.

In 3 of the patients, investigations show that renal function is normal apart from slight impairment of urinary acidification, compared with normal values obtained by Wrong and Davis (1959) in adults, and by Matsuda, Takeda, and Shida (1968) in children. However, both these groups used a somewhat larger dose of ammonium chloride (0·1 g./kg. body weight) than that given to our patients. This difference may also in part explain the reduced excretion of ammonia in our patients. Renal biopsy in 2 of these patients shows only a few deposits of calcium. Therefore if hypercalcaemia can be avoided in the future the outlook for these patients is good. One patient has severe renal damage. Creatinine clearance is reduced by half, and she is unable to acidify the urine satisfactorily after an ammonium chloride load. In the kidney biopsy specimen, half of the glomeruli are sclerosed and numerous deposits of calcium are present.

Glomerular damage in nephrocalcinosis has been reported previously by Mortensen and Baggenstoss (1954) who found that though the medulla was predominantly involved, glomeruli were affected in a quarter of the cases, showing both hyalinization and cellular proliferation. Glomerular involvement has also been reported in hypercalcaemia due to

(a)

(b)

FIG. 3.—*Renal biopsy from Case 1.* (a) *Several small deposits of calcium in the medulla.* (*Von Kossa.* × 66.) (b) *Three glomeruli with slightly increased cellularity.* (*PAS.* × 72.)

thyrotoxicosis (Epstein, Freedman, and Levitin, 1958) and in idiopathic hypercalcaemia of infancy (Lowe *et al.*, 1954; Dawson, Craig, and Perera, 1954). We therefore conclude that the glomerular damage in this patient is a consequence of the repeated episodes of hypercalcaemia. The degree of glomerular involvement appears to be out of proportion to the amount of calcium in the specimen. However, it has been shown that calcium is removed from deposits in the kidney when the serum calcium returns to normal (Kent *et al.*, 1958). This may well have occurred in this patient in the years since her last episode of hypercalcaemia.

Only one study of renal function and histology in children with vitamin D refractory rickets treated with large doses of vitamin D has been reported (Paunier *et al.*, 1968). 14 patients were studied, 13 of whom were found to have normal renal function. In 10 patients renal biopsy was performed and histology was normal in 8. One

(a)

(b)

FIG. 4.—*Renal biopsy from Case 2. (a) Several small deposits of calcium in the cortex. (Von Kossa. × 66.) (b) Four glomeruli, 3 of which are sclerosed and one partially sclerosed. (PAS. × 66.)*

patient with normal renal function had a moderate amount of calcium deposited in the medulla. The other patient whose renal function was impaired had sclerosed glomeruli and calcium deposits in the medulla. This patient had previously had a prolonged episode of hypercalcaemia and in addition suffered from chronic pyelonephritis. All these patients had had their vitamin D therapy carefully monitored by frequent estimations of the serum calcium which was maintained below 10·5 mg. 100 ml. as far as possible. Renal histology was also studied by Nigrin *et al.* (1962) in 8 patients with vitamin D refractory rickets treated with vitamin D, and 7 were found to have calcium deposits in the kidneys. Unfortunately renal function was not studied. The serum calcium level in these patients had not risen above 12·5 mg./100 ml. Robinson and Nelson (1945) found decreasing glomerular

FIG. 5.—*Renal biopsy from Case 3. (a) Two deposits of calcium. (Von Kossa. × 66.) (b) Two normal glomeruli. (Elastic van Gieson. × 66.)*

filtration rates in 2 patients with vitamin D refractory rickets treated with large doses of vitamin D.

The control of therapy in vitamin D refractory rickets is difficult, as the margin between the therapeutic and the toxic dose is small. Whereas the disease itself does not shorten life, nephrocalcinosis due to vitamin D intoxication may lead to chronic renal failure. It is therefore most important to avoid overdosage with vitamin D. Dent (1952) recommended that the serum calcium should be maintained below 11 mg./100 ml., and thought that 'biochemical cure' should be the aim of treatment. In vitamin D intoxication, the urinary calcium excretion rises above normal before the level of serum calcium rises. Hence Stearns (1964) based the control of therapy on the 24-hour urinary calcium excretion related to the calcium intake for a given body weight, and aimed to keep

the urinary calcium excretion between plus and minus 3 standard deviations from the mean urinary calcium excretion (Knapp, 1947). Stamp *et al.* (1964), in 52 patients, tried to maintain the serum calcium below 12 mg./100 ml., and found it was impossible to prevent the recurrence of deformities or restore a normal growth pattern. Pierce, Wallace, and Herndon (1964) believed that the serum calcium level was the most important criterion of impending toxicity, and regarded a level of 11 mg./100 ml. or over as an indication for withdrawal of vitamin D therapy. A rigorous programme of splinting was recommended to check the progression of deformities before puberty. Fraser and Salter (1958) and Paunier *et al.* (1968) recommended that the level of serum calcium should be kept below 10·5 mg./100 ml. but found that growth was not always in the normal range, nor was complete 'biochemical cure' obtained.

Therapy in our children has not been as successful as in those described by Paunier *et al.* (1968), and even mild hypercalcaemia for only a few months in Case 1 has caused early nephrocalcinosis. We have therefore reviewed the control of therapy in our patients to see how nephrocalcinosis can be avoided. We think that therapy should be controlled by frequent measurements of the serum calcium level which should be kept below 10 mg./100 ml. as far as possible. Though a serum calcium level between 10 and 11 mg./100 ml. may not be toxic, by aiming for a lower level the serum calcium level is unlikely to rise above 11 mg./100 ml. should overdosage with vitamin D occur. If hypercalcaemia does occur, simple cessation of vitamin D therapy alone may be inadequate, and cortisone should be administered as this has been shown to cause a rapid reduction of the serum calcium in vitamin D intoxication (Winberg and Zetterström, 1956). In view of the lack of correlation between the urinary calcium excretion and the development of nephrocalcinosis, we do not think that control of therapy should be based on the urinary calcium excretion. We think that neither complete radiological healing nor 'biochemical cure' should be the aim of treatment, and prefer to keep the serum alkaline phosphatase between 20 and 40 KA units. Despite these criteria, it appears that growth may be in the normal range with early diagnosis and treatment. Nephrocalcinosis is insidious in onset, and repeated renal biopsy is not practical as a means of detection. However, measurement of glomerular filtration rate every 6 months appears to be a practicable investigation, a falling glomerular filtration rate being an indication for a careful review of renal function and therapy.


## Summary

The danger of toxic effects of vitamin D therapy in children with vitamin D refractory rickets has been investigated by assessing renal function in 4 patients and renal histology in 3 of these patients who have been treated for many years with large doses of vitamin D and whose growth has been within the normal range. All the patients showed impaired ammonia excretion during an acid load test. Other renal function tests were normal in 3 patients, 2 of whom had a few calcium deposits in the kidneys. One patient showed definite impairment of renal function, and renal biopsy revealed that half the glomeruli were sclerosed, and that there were numerous deposits of calcium in the kidney. Control of therapy in this patient had been difficult, and 30% of monthly serum calcium measurements were over 11 mg./100 ml. There was no correlation between urinary calcium excretion and renal damage. We conclude that 'biochemical cure' and complete radiological healing should not be the aim of treatment in vitamin D refractory rickets, and that therapy should be controlled by frequent estimations of the serum calcium which should be kept below 10 mg./100 ml.


The patients were initially under the care of Professor O. H. Wolff, and we wish to thank him for allowing us to use the early information. We wish to thank Dr. N. Raine for advice with renal function tests, and the staff of his department for performing the biochemical measurements, Dr. A. H. Cameron for reporting on the renal biopsy specimens, Professor D. V. Hubble for his encouragement, and Dr. D. Fraser for allowing us to see the manuscript of his paper before publication.

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# *In Vitro* Studies of Vitamin D-Induced Aortic Calcification[1] (34148)

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The arterial calcification induced by the administration of large doses of vitamin D has been known and studied for many years. In the course of these studies, a great deal of morphological, histochemical, and biochemical data have accumulated which have been largely descriptive in nature (1–4). More recently, as new data have accumulated on the metabolism of Vitamin D and its mode of action, the manner in which this vitamin exerts its effects on osseous and calcium metabolism has been greatly clarified (5, 6). But with regard to the arterial calcification induced by hypervitaminosis D, two central problems remain. The first is whether the vitamin or one of its metabolites exerts a direct effect on the artery or whether the calcification is entirely a consequence of secondary changes in the composition of the extracellular fluids. The second is what factors are responsible for the peculiar and predictable distribution of arterial disease which hypervitaminosis D has in common with many other arteriopathies including human atherosclerosis (2). One approach to the study of this problem might be to assess the effects of sera of various compositions on arterial segments *in vitro*, isolated from general body metabolism. We here report the results of such a study which disclosed that the serum levels of calcium and vitamin D are both important determinants of the accumulation of calcium by such arteries and that the susceptibility of different arterial segments to calcification *in vitro* paralleled their susceptibility *in vivo* to some extent.

*Materials and Methods.* Two hundred g male Sprague-Dawley rats were used in all experiments except those involving rachitic animals. Sera were obtained by aortic puncture from animals lightly anesthetized with ether. Hypervitaminosis D was produced by injecting 200,000 units of Vitamin $D_3$ intraperitoneally three times weekly for 3 weeks. These rats, which were hypercalcemic and had extensive aortic calcification were the source of hypervitaminotic serum. Rachitic rat serum was obtained from 75 g male rats maintained for 3 weeks on Steenbock's rachitogenic diet no. 2 (7). Control sera for these experiments were from pair-fed animals of comparable weight on a stock diet. Two types of experimental systems were used. The first was an organ culture method in which 2-mm thick rings of thoracic aortas of rats were dissected free of surrounding connective tissue and placed on strips of cellulose acetate surgical burn dressing overlying metal rafts in Falcon organ culture dishes containing 2.2 ml of a nutrient medium consisting of 40% rat serum and 60% NCTC 109 tissue culture medium supplemented with 1000 units of penicillin and 1000 units of streptomycin/ml. The serum was from normal rats or rats with hypervitaminosis D. The cultures were refed three times weekly and were maintained at 37° in an atmosphere of 95% $O_2$ and 5% $CO_2$. After 1 week in culture, some rings were fixed in formalin, embedded in paraffin, and sections were stained with hematoxylin and eosin or the von Kossa reagent. Others were dried to constant weight at 104°, weighed, and ashed in sulfuric acid. Calcium was measured with an atomic absorption spectrophotometer and phosphate by the method of Fiske and Subba Row (8).

Since it soon became apparent that simple incubation of arteries in serum yielded results essentially similar to those obtained with organ culture, the method of Martin *et al.* (9) was used for most of the experiments. In this technique, segments of aortic arch,

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thoracic aorta, or abdominal aorta were dissected free of surrounding connective tissue, weighed and placed in 0.2 ml of serum/mg of wet weight of tissue. The serum contained 1000 units of penicillin and 1000 units of streptomycin/ml. The tubes in which the experiment was done were gassed with 95% $O_2$-5% $CO_2$, capped, and incubated at 37°. After the test period was complete the arteries were removed and chemical and histological studies were done in a manner identical to that used for the organ cultures.

*Results. Organ cultures.* With this technique the aortas appeared to be histologically viable, although small areas of focal necrosis were found even in control specimens, particularly at the sites of intercostal artery origin. Calcification was uncommon in control specimens cultured in medium supplemented with normal rat serum. In specimens cultured in medium supplemented with the serum of rats with hypervitaminosis D, calcification was uniformly much more extensive than in controls and occurred mostly in elastic tissue fibers and later in adjacent smooth muscle cells which were necrotic. Calcification was not observed in viable areas of the explant. There was no significant proliferative cellular response to these calcified areas which were largely in the media, often near the adventitial surface, and particularly advanced at sites of branching of intercostal arteries. This localization was perhaps related to the injury produced by the trauma of dissecting the surrounding periadventitial connective tissue during preparation. In keeping with the histological observations, chemical measurement showed that there was much more calcium in cultures maintained in medium containing serum from rats with hypervitaminosis D than in control cultures (Fig. 1).

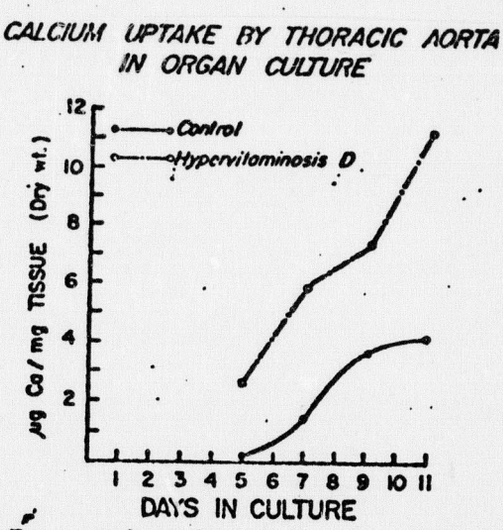


FIG. 1. arteries maintained in organ culture in medium supplemented with serum from rats with hypervitaminosis D accumulate more calcium than those maintained in medium supplemented with normal rat serum.

*Serum incubations.* In these preparations histological study indicated that by the second day of incubation, necrosis had begun and after 72 hr was virtually complete. When a timed study of calcium accumulation was done, the greatest increment of calcium accumulation occurred between 48 and 72 hr after incubation was begun if normal rat serum was used. In keeping with the observations of Martin *et al.* (9), calcification was virtualy restricted to elastic tissue lamellae when the vessels were studied histologically. Arteries incubated in serum from rachitic rats accumulated less calcium and phosphate than those incubated in control sera. Table I shows the results of this experiment. Except for experiments using rachitic serum, the results depicted in each Tables I–IV were reproduced in three repeated experiments. The $PO_4$ values varied similarly to those of calcium. When serum from normal rats and those with hypervitaminosis D were compared, it was found that if incubation was performed in serum from hypervitaminotic rats there was greater accumulation of both calcium and phosphate than with control serum (Table II).

TABLE I.[a]

| Serum | No. of samples | Mean[b] | SD[c] |
|---|---|---|---|
| Rachitic | 4 | 0.0019 | 0.00037 |
| Normal | 4 | 0.0065 | 0.0022 |

[a] Thoracic aortas of normal rats were incubated in serum for 72 hours. They accumulated more calcium from normal than from rachitic serum.

[b] (mg of Ca/mg of dry wt).

[c] Standard deviation.

TABLE II.[a]

| Serum | No. of samples | Mean[b] | SD[c] |
|---|---|---|---|
| Normal | 6 | 0.0017 | 0.0011 |
| Hypervitaminosis D | 6 | 0.0073 | 0.0018 |

[a] If thoracic aortas of normal rats were incubated for 72 hr in serum from normal rats or rats with hypervitaminosis D, they accumulated more calcium from hypervitaminotic serum.
[b] (mg of Ca/mg of dry wt).
[c] Standard deviation.

When large amounts of Vitamin $D_3$ (50 or 100 units/ml of serum dissolved in 0.01 ml of EtOH) were added to the serum and these sera compared with serum containing an equal weight of cholesterol dissolved in a similar amount of alcohol, no difference in the amount of calcium accumulated by either thoracic aorta or aortic arch was demonstrable. In agreement with the data of Martin *et al.* (9), addition of sufficient $CaCl_2$ to raise the level of serum calcium by 5 mg/100 ml also did not increase the amount of calcium accumulation. However, when both vitamin D and calcium were added to the serum in these amounts and comparisons made with serum containing equivalent amounts of cholesterol and NaCl, arteries incubated in the serum with added Vitamin D and calcium accumulated more calcium and phosphate than those incubated in control sera (Table III). Here, measurements were made both 48 and 72 hr after incubation was begun and the differences were present at both time intervals.

In experiments in which different segments of the aorta were compared, it was found that when segments of aortic arch, thoracic aorta or abdominal aorta were incubated in either normal serum or serum from rats with hypervitaminosis D and calcium measured in the arteries after 72 hr of incubation, aortic arch accumulated the most calcium, thoracic aorta slightly but not significantly less, abdominal aorta the least (Table IV). Calcium was measured in one set of arteries before incubation and no differences in calcium content of the three segments were found. Since histological studies indicated that calcification was virtually restricted to elastic tissue in these preparations, the amount of elastic tissue was measured in these portions of the aorta. This was done by the method of Hass (10) which uses warm 88% formic acid to digest the tissue elements which are not elastic. The isolated elastic tissue was then blotted dry, weighed, and the value was expressed as a percentage of the wet weight of the tissue. Table IV shows that the amount of elastic tissue in these three aortic segments paralleled the calcium accumulation in this incubation system.

*Discussion.* Superficially, at least, these data appear to provide clear-cut evidence that the composition of the serum is of primary importance in the pathogenesis of the arterial calcification induced by hypervitaminosis D and that both the hypercalcemia

TABLE III.[a]

| | 48 hr | | | 72 hr | | |
|---|---|---|---|---|---|---|
| | No. of samples | Mean[b] | SD[c] | No. of samples | Mean[b] | SD[c] |
| Serum + NaCl + cholesterol | 6 | 0.0014 | 0.002 | 6 | 0.0018 | 0.0007 |
| + Ca + cholesterol | 6 | 0.0013 | 0.0016 | 6 | 0.0023 | 0.0005 |
| + Vit. D + NaCl | 6 | 0.0007 | 0.0005 | 6 | 0.0023 | 0.001 |
| + Ca + Vit. D | 6 | 0.0048 | 0.0005 | 6 | 0.0042 | 0.0007 |

[a] As described in the text, addition of Vitamin D or calcium alone to serum did not influence the accumulation of calcium by thoracic aortas when incubated in such serum. If both calcium and Vitamin D were added, the aortas bound more calcium after either 48 or 72 hr of incubation.
[b] (mg of Ca/mg of dry wt).
[c] Standard deviation.

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TABLE IV.*

| Segment | Calcium accumulation | | | Elastica (%) | | |
|---|---|---|---|---|---|---|
| | No. of samples | Mean[b] | SD[c] | No. of samples | Mean[b] | SD[c] |
| Arch | 8 | 0.007 | 0.0004 | 5 | 70.0 | 6.4 |
| Thoracic | 8 | 0.006 | 0.0001 | 5 | 62.4 | 7.4 |
| Abdominal | 8 | 0.002 | 0.0005 | 5 | 23.8 | 6.6 |

* The amount of calcium accumulation by different arterial segments parallels the amount of elastin they contain.

[b] (mg of Ca/mg of dry wt).

[c] Standard deviation.

induced by Vitamin D and a direct local action of the vitamin itself are synergistic in contributing to the development of the lesion. There are, however, several qualifying points which detract from the strength of the data presented here. The first is the nature of the experimental system used. In it, whether simple serum incubation or an organ culture system was used, calcification was virtually restricted to areas of necrosis and even here was found restricted to elastic tissue fibers. In addition, even in the organ cultures, the distribution of calcification was primarily in the deep media in contrast to what is seen *in vivo*, where calcification usually begins in the inner elastic lammelae in major arteries (2). Even *in vivo*, however, calcification of viable smooth muscle cells is an uncommon event in the arteries which calcify under the influence of Vitamin D and elastic fibers are the first elective site of calcification (3). The differences in the mural pattern of calcification *in vivo* and *in vitro* are perhaps related to hemodynamic factors. Since the rat aorta contains no vasa vasora (11), its nutrition is derived from the luminal surface in an intact animal. In our systems, there was no flow or pressure and the nutrition of the tissue was by diffusion from all its surfaces. The adventitial trauma produced during dissection may also have contributed to the localization of the disease.

The observation that serum from hypervitaminotic animals or normal sera enriched with both vitamin D and calcium induced increased accumulation by the arteries as early as 48 hr after incubation was begun suggests that this was a true metabolic effect rather than something more nonspecific because necrosis was not yet advanced at this time.

The dosages of vitamin D added to the serum in these experiments was massive, and it might be argued that they are too far beyond the physiological range to be meaningful. However, this study was not designed to investigate the normal action of vitamin D but its toxic effects. It is more pertinent to point out that it has now been established that Vitamin D is normally converted in the body to 25-hydrocholecalciferol, a compound which has now been isolated and shown to be much more metabolically active than vitamin D itself *in vivo* (5) as well as in studies of organ cultures of bones (6). If it were used in a system such as this one, it might be possible to demonstrate an effect on arteries in lower dosage, and perhaps even without the addition of excess calcium to the serum.

*In vitro*, the arteries exhibited much the same sequence of calcification as they do *in vivo*, where calcification begins in the aortic arch and then spreads centrifugally (2). As expected, since the calcification was localized in the elastic tissue, the amount of elastic tissue in the artery paralleled the amount of calcium accumulation. The segmental distribution of many arterial diseases has often been considered to be related to local hemodynamic differences (11). These data, as do some others in the literature in studies of other arterial diseases (11) suggest that part of the hemodynamic effects on the distribution of arterial diseases are not primary, but are related to the morphological modifications

which pressure, flow, or turbulence induce in arteries both during embryonic development and in the adult. For example, elastic tissue develops most extensively in areas of pulsatile flow, and there is experimental data indicating that pulsatile flow through tubes inserted under rat skins can induce alignment of proliferated connective tissue elements into an organized structure having some of the morphological organization of an artery (12).

*Summary.* Arterial segments incubated in a culture system containing serum from rats with hypervitaminosis D accumulate more calcium than segments incubated in a system containing normal rat serum. If such arterial segments are incubated in serum, they accumulate more calcium from normal serum than rachitic serum and more from serum from rats with hypervitaminosis than from normal serum. Addition of either vitamin D or calcium alone to normal serum does not result in excess calcium accumulation by arteries incubated in such serum, but addition of both does. Different aortic segments accumulate different amounts of calcium, apparently in relation to the proportion of elastic tissue in the segments.

We wish to thank Dr. G. M. Hass for his encouragement and support.

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### INCONVÉNIENTS DE LA MÉTHODE

Elle ne souffre pas la médiocrité, car le moulage peut être marqué facilement : phlyctène, hématome, désunion ; si le moulage ne maintient pas un contact étroit entre le plâtre et la peau. Elle nécessite une constante surveillance. Si le plâtre serre trop, il faut pouvoir le refaire immédiatement. De même si au contraire, il devient trop lâche, car un contact étroit et permanent entre la peau et le plâtre est nécessaire pour éviter un œdème et tout hématome.

Nous changeons nos plâtres dès qu'ils deviennent lâches, et systématiquement au huitième jour. Le troisième plâtre sera fait au quinzième ou dix-septième jour, et l'on pourra alors retirer les fils cutanés. Ce plâtre conduira souvent jusqu'à l'appareillage définitif.

Cette méthode nécessite une parfaite collaboration entre le chirurgien, les rééducateurs, les infirmières et le prothésiste.

Nous avons utilisé cette méthode pour 18 malades :

— dans 8 cas, pour des amputations de cuisse pour tumeurs ou lésions septiques sous-jacentes ;

— dans les 10 autres cas, il s'agissait d'amputation de jambe ; 2 cas étaient des enfants qui venaient d'être amputés ailleurs, pour lésions traumatiques.

Cette méthode simple avec possibilité de réglage ultérieur nous a permis de garder ces amputés que très peu de temps et de les appareiller et rééduquer vite. Elle n'est pas sans risque, car les moulages devront n'entraîner aucune lésion sous jacente ce qui serait préjudiciable pour l'appareillage définitif.

## *DOSES ET RÉACTIONS THÉRAPEUTIQUES INHABITUELLES*

**LES PRESCRIPTIONS ABUSIVES DE VITAMINE D** peuvent aboutir à une intoxication caractérisée par des troubles digestifs : anorexie, nausées, vomissements, constipation, soif vive, par des troubles nerveux : tristesse, irritabilité, et par une atteinte de l'état général avec amaigrissement. L'hypercalcémie, dépassant 125 mg/l, l'hyperazotémie, avec ou sans acidose hyperchlorémique, la protéinurie avec hypercalciurie et cylindrurie forment le syndrome biologique. Des lésions rénales ou cérébrales irréversibles peuvent conduire à la mort, mais on obtient d'habitude la guérison avec la suppression de l'apport vitaminé, un régime pauvre en calcium et une corticothérapie. La prescription abusive de vitamine D n'est pas toujours le fait du médecin traitant, mais de la mère qui force les doses en pensant donner un « fortifiant », ou de plusieurs médecins, consultés successivement et qui ne se sont pas enquis des ordonnances antérieures. Les contre-indications de la vitamine D sont peu nombreuses. Elles sont représentées par les exceptionnelles affections avec hypercalcémie, par l'immobilisation des enfants paralysés ou suivant une cure orthopédique, chez qui on peut observer un syndrome de déminéralisation avec hypercalcémie et hypercalciurie. Chez les enfants atteints de l'exceptionnel rachitisme vitamino-résistant, on peut enfin passer facilement d'une posologie insuffisante à une posologie toxique (A. HENNEQUET, *Concours méd.*, 1969, 91, n° 45, 8158-8167). Rappelons qu'une posologie de 400 à 800 unités par jour, administrée sous forme de gouttes, est très souhaitable jusqu'à la fin du troisième mois de la vie. Au-delà, on peut prescrire tous les quatre à six mois une dose unique de deux milligrammes pour des raisons de facilité. Jusqu'à douze ou dix-huit mois, les prescriptions de vitamine D doivent figurer systématiquement sur le dossier médical de l'enfant.

**THROMBOSES ET CATHÉTERS INTRAVEINEUX.** — Des thromboses se sont formées chez 7 sujets sur 7 qui avaient eu des cathéters intraveineux laissés en place entre cinq et vingt-trois jours. Cette complication fut observée quels qu'aient été l'affection, le vaisseau ou le type de cathéter en cause et l'adjonction d'une thérapeutique anticoagulante ne servit à rien. Il est important de connaître ce fait et, tout en reconnaissant la nécessité fréquente d'introduire un cathéter, il faut connaître le danger thrombotique de cette technique (B. JACOBSON et D. SCHLOSSMAN *Radiology*, Août 1969, 93, n° 2, p. 355). On connaît aussi les dangers infectieux qu'entraînent souvent un cathéter laissé en place plus de cinq jours, la nécessité d'ensemencer tout cathéter suspect et l'interdiction de poser, sauf nécessité absolue, un cathéter aux membres inférieurs.

**COMPLICATIONS RETARDÉES D'APLASIE APRÈS CHLORAMPHENICOL.** — On sait que l'anémie aplastique développée après cet antibiotique peut guérir parfois, grâce à un traitement correct. A. J. SEAMAN rapporte deux complications survenues ultérieurement. Sa première malade, une fillette de 8 ans, avait reçu du chloramphénicol en Août 1961 pour une affection des voies respiratoires. Elle avait déjà été traitée, sans complications, par cet antibiotique, six mois auparavant. Au cours du deuxième traitement, apparut une urticaire ce qui mit fin à la thérapeutique, mais n'empêcha pas la survenue d'une anémie aplastique. Celle-ci guérit mais, en 1962, on nota 5 épisodes d'hémoglobinurie contemporains d'infections respiratoires. La seconde malade, âgée de 14 ans, reçut, en 1959, 1 g de chloramphénicol par jour pendant quatre jours et demi à l'occasion d'une lymphangite. On ne put découvrir si elle avait déjà pris cet antibiotique mais, en 1961, elle eut une anémie aplastique qui fut rattachée au chloramphénicol. Après une guérison apparente, la malade devait mourir de leucémie aiguë myélo-monocytaire en 1963. Bien que ces exemples ne soient pas absolument démonstratifs de la toxicité du chloramphénicol, on en déduisit que ces complications furent la rançon de mutations somatiques secondaires à l'intense activité mitotique développée pour repeupler les déserts médullaires (*Northwest medical*, Septembre 1969, 68, p. 831).

**CONSÉQUENCES PÉNALES DE LA THALIDOMIDE.** Une firme suédoise qui avait produit ce médicament a été condamnée à verser une indemnité annuelle, d'environ 114 000 dollars, et révisable avec l'index du coût de la vie, aux parents de cent enfants suédois et danois devenus infirmes. Toutefois, le directeur de la firme, qui avait accepté ce jugement pour faciliter le règlement de cette affaire et obtenir l'abandon des poursuites judiciaires, fait observer qu'il ne s'agit pas de blâmer la responsabilité d'un laboratoire ou d'une personne privée car ces accidents étaient dus seulement aux imperfections actuelles de la science (*Drug Trade News*, 20 Octobre 1969).

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# Hypervitaminosis D, anaemia and renal failure

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A 53-year-old English lady was referred in January 1967 because of reduction in renal function. The only symptom disclosed was an invariable nocturia and daytime frequency of micturition every 2 to 3 hr during the previous year. The past history included an 18 month history of variable anaemia of 7–10 g/100 ml (Table 1), unexplained by barium meals, gastroscopy and laparotomy. Study of the bone marrow in June 1966 showed normal cellularity, erythropoiesis was normoblastic with normal haemoglobinization; 10% of the white cell precursors were developing eosinophils. There had been no sustained response to iron, vitamin $B_{12}$ or folic acid.

*On examination*: no abnormality; BP 130/80; height 5 ft 4 in (160 cm); weight 47 kg.

Random and early morning urines were normal save for a specific gravity not exceeding 1010. Haemoglobin 8·8 g/100 ml; red blood count 3·1 m/mm³; MCHC 30%; MCH 28·7 γ-γo; MCV 96·7 cu μ; reticulocytes 3·5%; serum iron 105 μg/100 ml; total iron binding capacity 270 μg/100 ml; white

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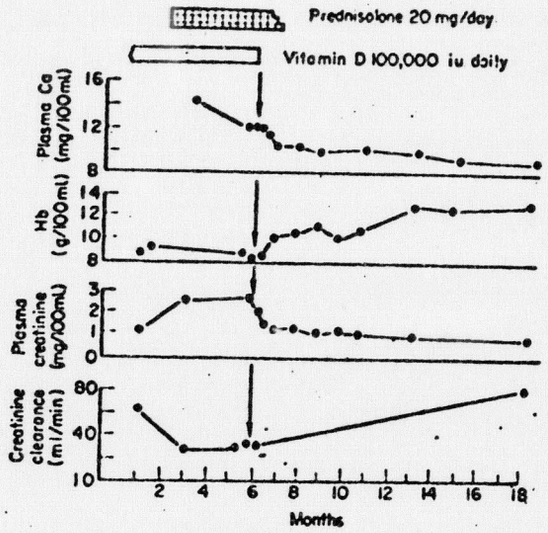


FIG. 1.

blood count 8000/mm³ with an eosinophilia of 850/mm³. Plasma creatinine 1·1 mg/100 ml and 24-hr creatinine clearance was 61 ml/min. Two weeks after the initial haematological measurements the eosinophilia was absent and the haemoglobin had risen to 9·4 g/100 ml with 0·8% reticulocytes. IVP: no anatomical abnormality of the renal tract. A percutaneous renal biopsy was performed: histology was compatible with either a focal and local glomerulonephritis with moderately severe nephron loss, or an interstitial nephritis with focal glomerular changes. Although positive serological evidence was absent, the combination of anaemia with reticulocytosis, transient eosinophilia and focal glomerular changes was suggestive of a systemic sensitivity phenomenon. On this basis prednisolone 20 mg/day was started.

Investigations were repeated after two months of corticosteroid therapy. The patient felt unwell, had headaches and anorexia. The haemoglobin was unchanged, the plasma creatinine had risen to 2·4 mg/100 ml and creatinine clearance fallen to 27 ml/min. Ampicillin (1 g/day) was added to the regimen on the basis that the renal interstitial changes might represent a chronic intrarenal infection. There was initially a short-lived improvement in well-being, but no change in renal function. Plasma calcium was 14·5 mg/100 ml, inorganic phosphate 3·6 mg/100 ml with a total protein of 6·7 g/100 ml. Serum alkaline phosphatase 5·2 KA units/100 ml. Urinary calcium 325 mg/day. (An 'average' diet was taken.)

The patient was re-admitted in mid-May of the same year for metabolic study. Renal function remained moderately severely impaired, plasma calcium was 12·8 mg/100 ml with a 24-hr urinary calcium excretion of 450-500 mg. Eventually the additional history was obtained that for the previous 7-8 years the patient had been regularly taking 100,000 i.u. of vitamin D daily, initially prescribed for finger nail splitting. From 31 May 1967, vitamin D was withdrawn and the prednisolone tapered off.

From being moderately unwell, the patient over a period of 2–3 weeks deteriorated markedly developing an agitated depression, requiring psychiatric advice as an in patient. Physical examination was negative, but as the plasma calcium at the time had fallen to 11·0 mg/100 ml, it was postulated that the symptoms were related to the changing plasma calcium. Accordingly 90 g of calcium gluconate were given intravenously. There was no change in condition. The depression yielded to trimipramine (Surmontil) over 1 month, during which the calcium fell to normal levels. Good health returned and was maintained after withdrawal of the antidepressant. The haemoglobin is now 13·6 g/100 ml, plasma creatinine 0·8 mg/100 ml, and creatinine clearance 85 ml/min (May 1970).

## Discussion

The chart demonstrates the biochemical and haematological improvement following withdrawal of vitamin D. During the hypercalcaemia and hypercalcuria the skeleton was radiologically normal. Densitometry measurements by Dr F. Doyle of Hammersmith Hospital of the distal 8 cm of the left and right ulna bones were 434 mg/cm³ and 402 mg/cm³ respectively. These figures are close to the normal mean for age (Doyle, 1961). There was therefore no evidence of bone sclerosis, and the ratio of trabecular to cortical bone was normal. Absence of sclerotic or other bone changes after 7–8 years of vitamin D consumption is surprising.

In some patients being investigated for renal disease the presence of calcium in needle biopsy tissue of the kidneys has led to the diagnosis of a parathyroid adenoma (Evans & Zutshi, 1962; Jockes, 1963). In reviewing the tissue we obtained from this patient, which included twenty-two glomeruli and 5 cm strips of medulla, we were impressed by the absence of any calcium deposits.

The severe renal functional impairment, to approximately one quarter of normal, recovered following withdrawal of the vitamin D and return of the plasma calcium to normal. The glomerular and interstitial changes must presumably be interpreted as caused by either the hypercalcaemia or some other effect of hypervitaminosis D.

The anaemia is of particular interest. With both acute and chronic renal failure a marked diminution in red cell mass occurs with shortening of the red cell survival time. Acute renoprival anaemia

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develops rapidly from the time of nephrectomy and does not appear to be related to the severity of the metabolic disturbance consequent upon the renal failure. In chronic renal failure, a clinically significant anaemia does not usually develop until the blood urea is persistently above 100 mg/ml or the creatinine clearance has fallen to less than 25 ml/min (Pryor & Jockes, 1969) although there is no direct relationship between the degree of nitrogen retention and the anaemia (Stewart, 1967). In the present case the serial blood ureas (Table 1) demonstrate that the anaemia is not dependent on the severity of the metabolic disturbance due to the renal involvement. It must be postulated that hypervitaminosis D is a direct or indirect cause of the anaemia, possibly acting by interfering with the renal production of some substance affecting erythropoiesis or red cell survival. Regrettably no observations were made of the red cell mass or red cell survival time. There is no evidence from patients with primary hyperparathyroidism that hypercalcaemia *per se* leads to an anaemia. We are unable to accept the view of Davies (1960) that with vitamin D poisoning 'an anaemia invariably occurs and is associated with the uraemia'. Scharfman & Propp (1956) described four cases in which vitamin D intoxication presented with a normochromic, normocytic anaemia. One of these patients, whilst anaemic, had normal renal function and the anaemia resolved on withdrawal of the vitamin. The fact that vitamin D causes an anaemia directly or indirectly in the presence of normal renal function is not demonstrated in the papers of vitamin D poisoning (Kaufman, Beck & Wiseman, 1947; Howard & Meyer, 1948).

TABLE 1. Female aged 53 years

| Date | Haemoglobin (g/100 ml) | Blood urea (mg/100 ml) |
|---|---|---|
| Jan 1964 | 13·0 | — |
| Aug 1965 | 9·8 | — |
| May 1966 | 9·8 | 30 |
| Sept 1966 | 7·4 | 63 |
| Oct 1966 | 14·0 | 46 |
| Jan 1967 | 8·4 | 50 |
| May 1967 | 8·2 | 94 |
| Oct 1967 | 11·0 | 59 |
| June 1968 | 13·6 | 43 |

It should be emphasized that the recovery of the haemoglobin concentration in our patient, followed withdrawal of the vitamin and occurred without any haematinics.

Vitamin D intoxication may present as a neuropsychiatric problem (Lehrer & Levitt, 1960) or mental depression may complicate a pre-existing hypercalcaemia (Chaplin, Clark & Ropes, 1951) on withdrawal of the vitamin the mental abnormality usually resolves (Anderson, Cooper & Naylor, 1968). In our patient there was no mental ill health until the vitamin was stopped and this was short lived.

## Acknowledgments

We wish to thank Miss F. Wadsworth, Medical Artist and Mr R. E. Bartholomew, Photographer, of the Institute of Urology for preparing and processing the charts. We are grateful to Dr G. A. Rose and his staff for the biochemical estimations.

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# Possible detrimental effect of large doses of vitamin D in familial hypophosphatemic vitamin D–resistant rickets

*Observations in presumably monozygotic twins with familial hypophosphatemic vitamin D–resistant rickets (FHVDRR) have shown that continued vitamin D therapy in one of the twins was associated with occurrence of pseudofractures and histologic evidence of active rickets; her untreated sister did not develop any pseudofractures, had a less severe defect histologically in bone mineralization, and had no evidence of an abnormally increased amount of osteoid. It is suggested that the efficacy of treatment of FHVDRR with high doses of vitamin D should be reinvestigated.*

Gunnar B. Stickler, M.D., Jenifer Jowsey, D.Phil., and Anthony J. Bianco, Jr., M.D.

ROCHESTER, MINN.

EVIDENCE has been presented[1] that vitamin D in large doses fails to influence the course of familial hypophosphatemic vitamin D-resistant rickets (FHVDRR), as far as growth, degree of bowing of extremities, or hypophosphatemia is concerned. On the basis of this observation we were encouraged to discontinue vitamin D therapy in one of a pair of presumably monozygotic twins with FHVDRR; the twin sister continued to take this medication.

This report shows that continuation of therapy in the one twin not only failed to show any benefit but was associated with the occurrence of pseudofractures and histologic changes of continued rachitic activity; these phenomena were not observed in the twin whose treatment had been discontinued.

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*Vol. 79, No. 1, pp. 68-71*

## CASE REPORTS

These twin girls were alike in appearance and their clinical courses were identical (Fig. 1). Our assumption that they were monozygotic twins was further supported by identical blood groups (13 subgroups). Their mother, 3 brothers, and 2 sisters have FHVDRR. The diagnosis of FHVDRR was made when the twins were 4 years of age. At that time they had bowing of their legs, roentgenologic evidence of rickets, and hypophosphatemia. Vitamin D therapy was started at a dosage of 350,000 I.U. per week and was gradually increased over an 11 year period to 800,000 I.U. per week (Fig. 1). There were no episodes of clinically recognized vitamin D intoxication.

See Editor's column, p. 181.

These twins had been the subjects of a previous study[2] of the effect of an increased oral in-

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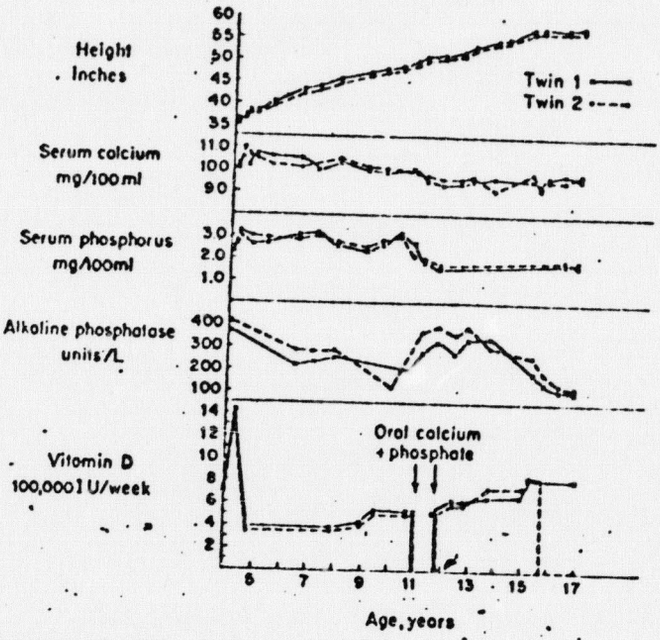


Fig. 1. Clinical courses of twins. Alkaline phosphatase is expressed in International units per liter (7 International units equal approximately 1 King-Armstrong unit). The dose of vitamin D is expressed in 100,000 I.U. per week; for instance, at 13 years the twins received 600,000 I.U. per week.

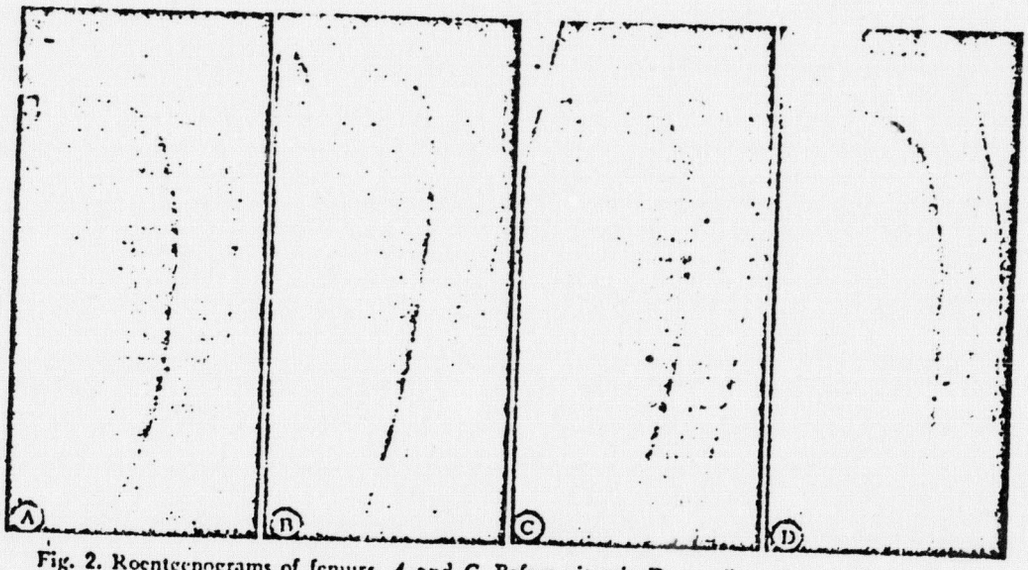


Fig. 2. Roentgenograms of femurs. *A* and *C*, Before vitamin D was discontinued. *B* and *D*, At follow-up 13 months later. *A* and *B*, Twin 2. *C* and *D*, Twin 1.

take of calcium and phosphorus without high doses of vitamin D; the same metabolic variables were measured in that study and in the present one and were almost identical.

When the twins were 15¾ years of age, vitamin D therapy was stopped for Twin 2 and continued for Twin 1 at a weekly dosage of 800,000 I.U. When Twin 1 was 16½ years of age, her vitamin D therapy was also stopped in preparation for corrective osteotomy. The twins were re-evaluated at age 17 years, just prior to the orthopedic procedure. The twins have had

Fig. 3. Twin 2 (treatment stopped). *A*, Mineralized bone section from trabecular area stained by the Paragon method. (×35.) *B*, Microradiograph of mineralized section. (×50.) The bone surfaces are fully mineralized as demonstrated by lack of staining in the section itself and the relatively white, dense appearance in the microradiograph. Incomplete mineralization around some osteocytes, which appear blurred, indicates a previous episode of rickets.

no further therapy following corrective surgery and had not experienced any new symptoms when seen 1 year later.

## RESULTS

No differences were observed between the twins in regard to subjective symptoms, height, or serum calcium, phosphorus, and alkaline phosphatase values, either during vitamin D therapy or after this therapy was discontinued in Twin 2.

Roentgenograms at age 15¾ years showed no pseudofractures in either twin. However, with continuation of high doses of vitamin D in Twin 1, pseudofractures of the femur were noted first at age 16⅓ years and again at age 17 years (Fig. 2). Twin 2 did not have pseudofractures.

Because of the marked femoral bowing, segmental femoral osteotomies were performed in both twins at the age of 17 years, and biopsy specimens of bone were obtained. In Twin 2 (treatment stopped) there was clear evidence of areas of low mineral density around the osteocytes, indicating a history of rickets (Fig. 3), but there was no abnormal amount or thickness of osteoid tissue, suggesting that active rickets was not present at the time of biopsy. This was in contrast to the findings in Twin 1, who was receiving vitamin D therapy; both the calcified sections and the microradiographs demonstrated clear evidence of an extensive long-term failure of calcification (Fig. 4). There were areas of low mineral density around osteocytes, lack of calcification of the cement lines, and broad osteoid borders. There appeared to have been some periods of improvement in the past, as indicated by the appearance of normal bone covered by abnormal tissue.

## COMMENT

We considered the possibility that the finding of roentgenologic and histologic evidence of rickets only in the twin whose therapy had been continued was an error due to mislabeling of specimen and roentgenograms. However, the mislabeling would have had to have occurred on 3 separate occasions (2 roentgenologic examinations and the biopsy) and is therefore not likely. The fact that the previous courses of the 2 girls had been almost identical makes the assumption of a variation in the natural course of the disease unlikely. One is left with the possibility

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Fig. 4. Twin 1 (treatment continued). *A*, Mineralized bone section from trabecular area stained by the Paragon method. (×35.) *B*, Microradiograph of mineralized section. (×45.) Dark-staining borders on surfaces of trabeculae in the section and fuzzy appearance in the microradiograph indicate unmineralized and partially mineralized bone. Such an appearance indicates active rickets.

that, in one of the twins, vitamin D not only failed to improve the condition but seemingly worsened it.

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# Toward better therapy for resistant rickets

THE OBSERVATION of Stickler and associates, recorded elsewhere in this issue, that administration of vitamin D in high dosage to a patient with resistant rickets was associated with the continuing presence or worsening of the rachitic lesion has not been paralleled in the experience of others. The authors observed that one of a pair of identical twins given 600,000 I.U. of vitamin D weekly developed pseudofractures and had histologic evidence of rickets in a bone biopsy while the other twin, receiving no vitamin D, had no evidence of these changes. As the authors state, such a paradoxical effect does nothing to increase one's esteem for vitamin D as the sole agent for the treatment of this disease. Obviously the usual effect of vitamin D is to increase bone density and prevent further deformity, but all who manage patients with this disease are aware of the hazards of its use and the limitations of its value in treatment.

Fortunately, 2 recent developments may go far to ease the way of the rickets therapist and to improve the outlook for these patients. About 15 years ago Fraser and associates[1, 2] demonstrated that constant infusion of phosphate would heal either resistant or deprivational rickets without recourse to therapy with vitamin D. This observation was of great interest but had little practical value until it was shown[3-5] that administration of a phosphate supplement orally would allow healing of rickets when vitamin D was given concurrently in doses in the range of 25,000 to 75,000 I.U. daily, a range which rarely results in intoxication. In 2 of the studies,[4, 5] the effect of the oral phosphate has been dramatic in healing long-standing, severe rickets and osteomalacia. Continuing the regimen of phosphate and vitamin D after the rickets have healed has been successful in preventing recurrences.[3] The result is much smoother management of the patient; management with vitamin D alone frequently required such large doses that intoxication occurred with healing of the rickets and, as the dose was reduced, the rickets was reactivated with the risk of producing further deformity. These 2 extremes can now be avoided. Long-term use of the combined phosphate-vitamin D regimen in our clinic has resulted in virtual disappearance of rachitic deformity in one patient who had very severe rickets as a small child. In addition, recent observations of our patients treated over long periods of time (as yet unpublished[6]) indicate that in some, acceleration of growth may be produced by combined therapy, providing a dose of vitamin D is given which is somewhat greater than that needed to heal or maintain the healing of the rachitic lesions. The main disadvantage of the phosphate therapy is the frequency with which doses of the medication must be given. The optimal regimen is probably a dose 6 times daily but one often has to settle for 4 or 5 doses daily. No toxic side effects have been noted except for mild-to-moderate diarrhea appearing in the first few days after the therapy is started and disappearing despite continuing the regimen.

See related article, p. 68.

The second development which may revolutionize therapy is a much more recent one and not as yet fully evaluated. It has been found by Blount and associates[7] that the active metabolite of vitamin D is 25-hydroxycholecalciferol (25-HCC). In some if not all patients with vitamin D-resistant rickets, this metabolite is formed only in

limited quantities or not at all when vitamin $D_3$ is given.[8] Whereas it has been reported[9] that administration of this metabolite over periods of one month has no effect on calcium or phosphate balance in patients with D resistance, others[8, 10] have reported that it does influence calcium metabolism and is effective in producing healing of the lesions. These reports[8, 10] indicate that its duration of action is short as compared to that of vitamin $D_3$. Discontinuing administration of the agent causes rapid reversion to a negative calcium balance and thus a therapeutic regimen employing the agent should be subject to rapid, fine adjustments as compared to the slow response to changes in vitamin D dosage. Toxicity should therefore be avoidable or quickly reversible. Whether use of this agent will promote growth in these children has not been determined.

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# ASSOCIATION BETWEEN AORTIC STENOSIS AND FACIES OF SEVERE INFANTILE HYPERCALCÆMIA

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THE severe form of infantile hypercalcæmia, first described by Fanconi et al. (1952), consists in failure to thrive, mental retardation, a characteristic facies, and often a convergent squint; a systolic murmur is present in most cases. The hypercalcæmia is usually severe and accompanied by a raised blood-urea and other evidence of renal damage. The skull base is thickened and densely calcified, and there are similar areas of dense calcification in the vertebræ, metaphyses of the long bones, and many of the epiphyses.

In a review of this condition Schlesinger et al. (1956) pointed out that, although death might occur early in the disease from renal failure and hypertension, occasionally renal function was partly or wholly restored. There has been no long-term study of the results of infantile hypercalcæmia, but Mitchell (1960) has shown that of thirteen children examined 3–6 years after the onset of the hypercalcæmic phase, all but one were normal in height, mentality, and renal function; the one exception was slightly retarded mentally at the age of 5½, but Mitchell considered that the facies (squint, epicanthic folds, and prominent upper lip) was indicative of the severe type of hypercalcæmia, whereas the other twelve children were thought to have had the mild or benign form of hypercalcæmia. Observation of our early cases of the severe form of infantile hypercalcæmia over the past few years has shown that the systolic murmurs have become characteristic of aortic stenosis, and that progressive renal impairment and hypertension are likely to appear. Familiarity with the facial appearance of these cases as they have developed has enabled us to recognise for the first time the clinical picture in five children aged 8–14 years who attended the heart clinic with aortic systolic murmurs. Retrospective assessment of their early case-histories shows many of the characteristic features of infantile hypercalcæmia.

## Case-records

### Case 1

A girl, born on June 18, 1947, was an only child. Her mother was asthmatic; her father was healthy. Pregnancy and delivery were normal. The mother's intake of vitamins during pregnancy was normal. Her birthweight was 5 lb. 9 oz. (2·52 kg.). The child was breast-fed for 6 weeks. At 3 months she began to vomit, became difficult over her feeds, and passed one or two small hard stools daily. She was given the usual vitamin supplements during infancy.

The child was first seen at The Hospital for Sick Children at the age of 6 months. She was a miserable, restless, hypotonic baby who weighed 11 lb. 4 oz. (5·1 kg.). Her head circumference was 15 in. (37·5 cm.). A loud systolic murmur was heard over the precordium, the femoral pulses were easily palpable, and the blood-pressure was 150/90 mm. Hg.

*Investigations.*—Urine, protein 20 mg. per 100 ml., 1–5 white cells per high-power field. Blood-urea, 70 mg. per 100 ml. Blood-cholesterol, 163 mg. per 100 ml. X-ray chest, transverse heart. Intramuscular pyelography showed poorly defined renal pelves; no evidence of nephrocalcinosis.

Electrocardiography (E.C.G.): inverted T waves in lead I, and depression of ST in leads II and III, indicating myocardial damage.

At 10 months the murmur was unchanged. The E.C.G. now showed left ventricular hypertrophy, but screening showed a normally shaped heart. At the age of 2 years 11 months scoliosis, which has required orthopædic treatment ever since, was noticed.

At the age of 9½, when attending the heart clinic the child was seen to have the "hypercalcæmia" facies (fig. 1). She had a grade-II early ejection murmur loudest to the left of the sternum. Her blood-pressure was 170/80 mm. Hg. Her head circumference was 19¾ in. (49 cm.). She was attending a special school because of mental backwardness. The urine now contained 200 mg. protein per 100 ml.; blood-urea was 87 mg. per 100 ml.; and the E.C.G. showed gross left ventricular hypertrophy.

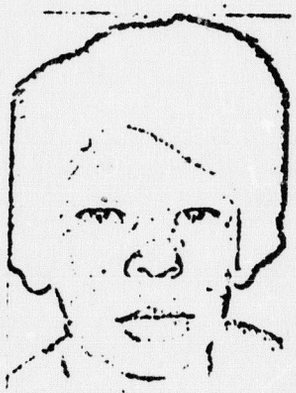

Fig. 1—Case 1, aged 10 years.

X-ray of the skull, spine (apart from the scoliosis), and long bones showed no abnormality. At 12 years her blood-pressure had increased to 170/125 mm. Hg. and the urine contained between 500 and 2000 mg. of protein per 100 ml. with a moderate number of epithelial cells. Her blood-urea rose to 200 mg. per 100 ml. in the next 2½ years; the murmur was now a grade-III ejection murmur, and for the first time a systolic thrill was felt over the right carotid artery. Since then both murmur and thrill have become less obvious, though the patient's blood-pressure has continued to rise. She was admitted to the hospital in January, 1963, aged 15, with facial weakness and slurred speech which seemed to be the result of an acute cerebrovascular accident. Her blood-pressure was 260/200 mm. Hg, haemoglobin 48%, and blood-urea 312 mg. per 100 ml. The patient's condition improved slightly and she was discharged home where she died a month later. Necropsy was not performed.



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Fig. 2.

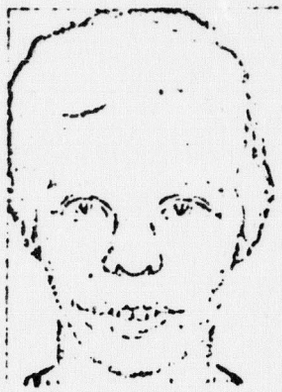

Fig. 3.

Fig. 2—Case 2, aged 2½ years.

Fig. 3—Case 2, aged 15½ years.

*Comment*

The past history here was very suggestive of hypercalcæmia with early renal damage. A systolic murmur was already present at the age of 6 months. Subsequently the hypertension and the renal damage gradually progressed. There is no proof that the murmur was due to aortic stenosis, but this is likely. Mental retardation was pronounced, and the facies resembled those of known cases of the severe type of hypercalcæmia.

**Case 2**

The patient was a girl born on April 26, 1945, of healthy parents. An older child was healthy. Pregnancy and delivery were normal; the mother took cod-liver oil capsules in the usual dosage for the last 6 months of her pregnancy. The child's birthweight was 6 lb. 3 oz. (2·8 kg.). She was bottle-fed with numerous changes of milk because of poor appetite and inadequate gain in weight. At the age of 3 weeks a systolic murmur was detected; she first attended The Hospital for Sick Children when she was 5 months old; a blowing systolic murmur was heard, loudest in the pulmonary area.

At the age of a year a squint was noticed. The child had normal vitamin supplements during infancy, and orthodox doses of 'Virol' and 'Multivite' tablets were prescribed at a welfare clinic from the age of 1⅓ to 2½ years (fig. 2). She had loose offensive stools between the age of 2 and 3 years, and cœliac disease was suspected. A systolic thrill was noticed for the first time at 4½ years.

The child was admitted to hospital for further investigation when she was aged 6 years 11 months. She was backward mentally; there was a systolic murmur and thrill conducted into the neck and the blood-pressure was 120/80 mm. Hg. Her heart was not enlarged clinically or radiologically, and E.C.G. suggested right axis deviation. Her I.Q. at 7 years 3 months was 62%. From the age of 8 years 10 months the child's blood-pressure began to rise slowly. Electrocardiographically left ventricular hypertrophy was first detected at 10 years, and this gradually increased during the period of observation. Cardiac enlargement was first noticed clinically in the following year.

The child was admitted at 13 years 11 months for further investigation; her blood-pressure was 150/90 mm. Hg, and X-ray showed considerable cardiac enlargement to the left; ventricular puncture with simultaneous pressure readings in the left brachial and right femoral arteries showed a pressure gradient of 40 mm. Hg across the aortic valve indicating mild stenosis. The "hypercalcæmia" facies was first recognised during this admission (fig. 3).

*Investigations.*—Urine, protein 40 mg. per 100 ml., many squamous epithelial cells, 50 white cells per c.mm. in uncentrifuged urine; urine concentration and dilution test normal. Blood-urea 30 mg. per 100 ml. Intravenous pyelography normal, except that the right kidney seemed slightly smaller than the left.

Later the child's blood-pressure rose to 150/110 mm. Hg at the age of 16 years. 9 months later she was referred to the late Dr. Paul Wood at the National Heart Hospital. Her blood-pressure had now fallen to 140/90, and there was electrocardiographic evidence of increased left ventricular strain. A retrograde aortogram showed a supravalvar stenosis. She was operated on by Mr. O. S. Tubbs on July 24, 1962. The stricture seemed to consist of thick "myxomatous" tissue; it was incised, and a 'Teflon' graft was sutured into the defect made by the incision. She died the next day.

*Necropsy*

At necropsy the operative findings were confirmed. The thickening and narrowing of the aorta extended to the bifurcation. The aorta was narrowed between the origin of the left subclavian artery and site of the obliterated ductus. The left ventricle was hypertrophied by about half. The kidneys seemed normal. Microscopic examination of the aorta (Dr. D. K. Henry) showed thickening and fibrosis of the media with some deficiency of the muscle and elastic tissue. The stenosis was due to a combination of grossly thickened media and a projecting circumferential ridge of dense fibrous tissue apparently of intimal origin; at this point the elastic tissue was almost absent. Below the stenosis the intima was thickened and showed early atheromatous change. The aortic valve appeared slightly thickened by an increase in fibrosis, but was otherwise normal. The kidney was normal, except for congestion and a small cortical infarct; there was no calcification.

*Comment*

The early history of feeding difficulties suggests idiopathic hypercalcæmia. It is of interest, from the ætiological point of view, that the murmur was already present at the age of 3 weeks.

**Case 3**

This boy was an only child, born on May 12, 1951, of healthy and unrelated parents. The pregnancy was complicated by pre-eclamptic toxæmia, but the delivery was normal. The child's birthweight was 5 lb. 10 oz. (2·55 kg.). The mother's vitamin intake was normal during pregnancy. The baby was breast-fed for 5 or 6 months; but there was some vomiting during the first 2 years, and he did not take mixed feeding until he was aged 10 months. He sat alone and began to speak when he was a year old, and could not walk without aid until aged 1 year 11 months. His vitamin-D intake was normal during his first year. In infancy he was thought to be backward, and a cardiac murmur was first detected at the age of 3 months.

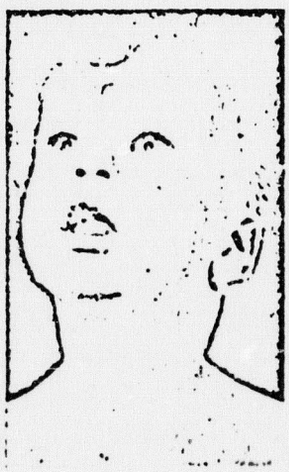

Fig. 4.

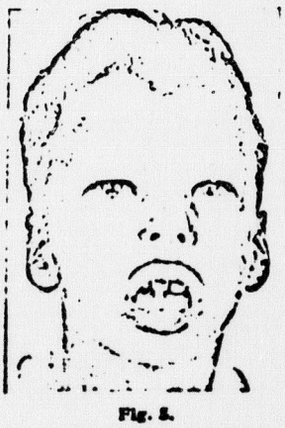

Fig. 5.

Fig. 4—Case 3, aged 2 years.

Fig. 5—Case 3, aged 8 years 11 months.

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The child was first seen at The Hospital for Sick Children at 1 year 11 months when he weighed 21 lb. (9·5 kg.) and his height was 30 in. (75 cm.); he was noticed to have a "peculiar" facies (fig. 4) and there was a loud systolic murmur most audible in the third left interspace. His blood-pressure was 100/60 mm. Hg, and the femoral pulses were normal. The child gained weight slowly. His blood-pressure remained normal until he was aged 8 years 11 months, when it rose to 155/90 mm. Hg. He was screened on three occasions; the pulmonary artery was initially thought to be small, but the heart shadow was normal throughout. E.C.G. recordings during the period of observation showed no significant abnormalities. At the age of 8 years 11 months he was recognised as having the "hypercalcæmia" facies (fig. 5) and was further investigated.

*Investigations.*—Urine, normal to routine testing. Blood-urea, 41 mg. per 100 ml. Serum-calcium, 9·8 mg. per 100 ml. Serum-cholesterol, 200 mg. per 100 ml. X-ray of skull and long bones normal; no evidence of nephrocalcinosis in the abdomen.

When the child was last seen at the age of 10 years 10 months his blood-pressure was 190/100 mm. Hg, and for the first time a systolic thrill was felt in both carotids. The boy has always been somewhat backward, and is two years behind at school (C stream).

*Comment*

This boy has an early history of feeding difficulties. Besides increasing hypertension there is evidence of a probable aortic stenosis. His facial appearance is typical, and he is somewhat backward mentally. No formal tests of renal function have been performed.

Fig. 6—Case 4, aged 8 years.

Fig. 7—Case 4, aged 16 years.

Fig. 8.

Fig. 8—Case 5, aged 1 year.

Fig. 9.

Fig. 9—Case 5, aged 13 years.

## Case 4

The parents of the 4th child are first cousins and healthy. There are two normal brothers. The mother's pregnancy and labour were normal; the child's birthweight was 6 lb. 8 oz. (2·59 kg.). He was breast-fed for 6 weeks; then, because of vomiting, he was changed to bottle-feeding with a variety of milks, but the vomiting persisted. He never took cod-liver oil properly, and at the age of 2 months was started on halibut-liver oil which he was still taking at the age of 2 years 11 months in a dose of 6 drops daily. Between the age of 6 months and 2 years 6 months he was given thyroid extract, but the dose is not known. He did not sit until he was 9 months old, but he stood at the age of a year. At 2 years 6 months he had begun to walk and was saying single words.

The child was first seen at the age of 2 years 11 months at The Hospital for Sick Children. He weighed 25 lb. (11·3 kg.) and his height was 34½ in. (86 cm.). The left palpebral fissure was wider than the right, and there was an epicanthic fold on the left side; there was no squint. The boy's heart was not enlarged clinically, but a systolic murmur was heard, loudest at the pulmonary area and conducted up into the neck and to the back. A systolic thrill was felt in the neck. X-rays of his chest and skull were normal, and screening of his chest showed a normal cardiac outline. E.C.G.s showed no significant abnormality. Fig. 6 is a photograph of the boy at the age of 8 years. At the age of 14 years 11 months he was suspected of having the "hypercalcæmia" facies. His blood-pressure remained normal, except for one outpatient reading of 140/80 mm. Hg at the age of 16. He had always been recognised as being backward and attended a special school.

At the age of 16 years 2 months (fig. 7) the boy was admitted to University College Hospital under Prof. M. L. Rosenheim for further assessment. His height was 5 ft. 6 in. (165 cm.) and his head circumference was 20½ in. (51 cm.). His heart was of normal size, and an aortic ejection murmur was heard which was thought to be due to aortic stenosis, though no thrill was recorded. The boy's blood-pressure initially was 130/80 mm. Hg, but settled to 110/60 on rest in bed. He did not complain of thirst, but had to get up twice each night to pass urine.

*Investigations.*—X-rays of skull and long bones were normal, and there was no radiological evidence of nephrocalcinosis. Specific gravity of the urine was 1·017 at the highest reading on fluid deprivation; urea-clearance normal. Blood-urea normal. Serum-calcium 10·5 mg. per 100 ml. on two occasions. E.C.G. normal. Intelligence quotient 46%.

*Comment*

The boy's early history of feeding difficulty could well be explained by hypercalcæmia. There is reasonable but not conclusive evidence of aortic stenosis, but this is presumably very mild as the E.C.G. has always been normal. There is only suggestive evidence of slight renal insufficiency; his intelligence is very low.

## Case 5

The parents of this boy, born on Jan. 24, 1946, were healthy and unrelated. One younger sister is quite normal. The mother's pregnancy was normal, and she took the usual vitamin supplements during the last 6 months of pregnancy. Delivery (at term) was normal and the birthweight was 6 lb. (2·7 kg.) The baby was breast-fed for 6 months, with no feeding difficulties. During the first year (fig. 8) gain in weight was satisfactory but slowed up after this, and by the age of 3 years he weighed the same as his healthy 19-month-old sister. His vitamin-D intake was not excessive during the first 3 years of life.

A murmur was first discovered at 2 years 3 months when he attended the Royal West Sussex Hospital (Dr. G. A. Emmerson) because he was not walking. He weighed 22 lb. 15 oz. (10·4 kg.) and was seen to have an abnormal facies ("marked epicanthic folds"). A loud systolic murmur was heard, loudest over the right first interspace and conducted up into the neck and

Fig. 10—Case described by Schlesinger et al. (1956) aged 1 year 9 months.

Fig. 11—The same case as in fig. 10, aged 11 years.

posteriorly; the femoral pulses were palpable. Screening of the patient's chest and E.C.G. were both normal. He was thought to be backward mentally. At the age of 3 years 3 months a thrill was noted over the upper part of the sternum, and an aortic lesion was suspected; his blood-pressure was 110/60 mm. Hg. At the age of 4 years the boy attended The Hospital for Sick Children.

There was no change in his physical signs. There was no cardiac enlargement clinically or radiologically, but the E.C.G. showed inversion of the T wave in lead I and low take-off in lead II. At 6 years the blood-pressure was 90/60 mm. Hg. There was no E.C.G. evidence of ventricular hypertrophy and no axis deviation; U waves were present in $V_3$. The boy's I.Q. at this time was 69%. 2 years later his condition was unchanged clinically, but the E.C.G. showed flat T waves in lead I and evidence of left ventricular hypertrophy with left ventricular strain. When he was seen at the age of 14¾ years his blood-pressure was 120/90 mm. Hg, and the E.C.G. now showed only slight left ventricular hypertrophy and possible right bundle-branch block. He was then seen to have the facies of the severe type of hypercalcæmia (fig. 9). No renal function tests were done, but there was no complaint of polyuria or thirst. At 17 years, when he was seen at the Brompton Hospital (Dr. R. G. Gold), his blood-pressure had risen to 180/100 mm. Hg.

*Comment*

In this boy, weight gain was apparently normal for the first year. There is no evidence of renal insufficiency, but it has been impossible to test renal function. The physical signs suggest aortic stenosis. There is clear evidence of mental retardation, and the boy has the characteristic facies.

## Discussion

In each of these five cases the clinical features correspond very closely to those of the older surviving cases of infantile hypercalcæmia of the severe type (Schlesinger et al. 1956). All five children presented as a problem in cardiac diagnosis, but direct proof that they were ever hypercalcæmic is lacking. Renal biopsy to look for evidence of nephrocalcinosis, which is nearly always present in infantile hypercalcæmia (Schlesinger et al. 1956), did not seem justified.

We have direct evidence of aortic stenosis in one case only (case 2), and here the valves were normal and the stenosis was supravalvar in type. The cause of the systolic murmur in the severe type of hypercalcæmia has been much discussed; but in two of the cases (see figs. 10 and 11) originally described by Schlesinger et al. (1956) the physical signs now suggest aortic stenosis and resemble those in our cases. Necropsy studies in some cases have shown that valvular changes are present. In one case (Dawson et al. 1954) a systolic murmur and hypertension were found, but post mortem there was no abnormality of the valves or myocardium. Fletcher (1957) found a calcified aortic valve in a child who had had both hypertension and a systolic murmur, and Schlesinger et al. (1956) reported another case with a systolic murmur without hypertension in which there was a calcified area in the mitral valve. Joseph and Parrott (1958) found thickening, without calcification, of the edges of the mitral and tricuspid valves, and some fibrous thickening of the aortic valve in another case where the blood-pressure had not been recorded during life. One of the best descriptions of the changes in the aortic valve in the severe type of hypercalcæmia was given by Rashkind et al. (1961), who found at necropsy that the valves were thickened and yellowish; microscopically the thickening was due to "myxœdematous" connective tissue. The coronary arteries also showed a similar thickening of their walls. There was no calcification in the aorta, aortic valves, or coronary arteries.

In the early stages rigidity of the valves seems likely to be a common cause of the systolic murmur, and hypertension alone to be an uncommon cause. In view of these findings, it is difficult to see why the murmur should disappear in cases where the blood-pressure has been normal, as in a patient of Russell and Young (1954) in whom the murmur disappeared as the child's clinical condition improved. Rinvik (1957) described a similar case, also without hypertension. The evidence does suggest, however, that a thickening of the valves rather than calcification is the primary abnormality and that the changes may affect other large arteries.

It would be inappropriate to discuss the aetiology of infantile hypercalcæmia here, but it may be significant that the systolic murmur was detected as early as 3 weeks after birth (case 2), at 3 months (case 3), and at 6 months in two others; in one of these two (case 1), hypertension and renal damage were already present.

Though the connection between aortic stenosis and previous hypercalcæmia has not been reported Williams et al. (1961) and Beuren et al. (1962) have described some cases of supravalvar stenosis said to be congenital, combined with mental retardation and a peculiar facies. Systemic hypertension was not recorded in any of these cases. From the facial appearance of the children in the published photographs it seems probable that these workers are describing the same condition that we have studied, though they had evidently not considered infantile hypercalcæmia as a possible cause.

Our case 2 had a lesion identical with that described by Williams et al. and by Beuren et al., but we were unable to find any microscopic evidence of previous hypercalcæmia; so the connection between this condition and infantile hypercalcæmia cannot be proved at this stage. But possibly the thickening from "myxomatous" or "myxœdematous" tissue may sometimes involve the aortic valve and sometimes the aorta immediately above the valve.

We wish to thank Dr. Bernard Schlesinger and the Editor of the *British Medical Journal* for allowing us to reproduce the photographs of the case of infantile hypercalcæmia; and Prof. M. L. Rosenheim and Dr. G. A. Emmerson for supplying further information about cases 4 and 5. We would also like to acknowledge the courtesy of Mr. O. S. Tubbs for allowing us to quote from his operation findings; and Dr. D. K. Henty for her histological report.

*References at foot of next column*

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# ENCEPHALOPATHY AND FATTY DEGENERATION OF THE VISCERA A DISEASE ENTITY IN CHILDHOOD

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THIS report describes the clinical and pathological features of a group of twenty-one children admitted to the Royal Alexandra Hospital for Children between March, 1951, and March, 1962, who appear to have had an illness which, we believe, represents a clinicopathological entity. We shall refer to this condition as fatty degeneration of the viscera, of unknown cause.

The outstanding clinical features were profoundly disturbed consciousness, fever, convulsions, vomiting, disturbed respiratory rhythm, altered muscle-tone, and altered reflexes. The onset was usually associated with cough, rhinorrhœa, sore throat, or earache. There was often hypoglycæmia and a low cerebrospinal fluid (C.S.F.) glucose, and the serum glutamic-oxalacetic acid transaminase (S.G.O.T.) and serum glutamic-pyruvic acid transaminase (S.G.P.T.) levels were increased in each of the seven patients in whom they were measured.

Seventeen of the children died, and at necropsy remarkably uniform pathological changes were found. To the unaided eye, these were expressed as cerebral swelling, a slightly enlarged, firm, and uniformly bright-yellow liver, and pallor and slight widening of the renal cortex.

## Clinical Features

The series consisted of fourteen girls and seven boys. The youngest was 5 months old, and the eldest 8½ years. Fourteen of the twenty-one were aged 2 years or less, and the other 7 were over 5 years.

The frequency of the main clinical features and the laboratory findings is shown in the tables.‡ There was usually an initial period of malaise, often with cough, sore throat, earache, or rhinorrhœa, and the children did not seem very ill. Usually after 1 to 3 days, but varying occasionally to 2 or 3 weeks, there was fairly abrupt clinical deterioration, the most worrying changes being persistent severe vomiting and the onset of stupor or coma, sometimes followed by convulsions. In ten of the fourteen children who had upper-respiratory tract symptoms, there was a short period of apparent recovery before symptoms returned and the more serious phase of the illness supervened.

In nearly half the group there was wild delirium, with screaming, intense irritability, and violent movements, during the period when consciousness was deteriorating, and in several of the other children an unusual degree of restlessness was noted.

On admission to hospital, all but two of the patients were already stuporose or comatose. Eight exhibited, at some time afterwards, the delirium described above. Usually one or more of the features that we have learnt to regard as characteristic, such as hyperpnœa or a low C.S.F. glucose, was present at or shortly after admission, and others appeared over the ensuing 12 or 24 hours.

Every patient had profoundly disturbed consciousness, and seventeen had seizures. The types of convulsion varied, and some patients had more than one sort of fit at different times. Focal twitching and tetanic spasms were seen most often, and in three patients, one of whom had opisthotonus, the spasms were sufficiently like tetanus for this diagnosis to be considered. Convulsions were often difficult to control; in ten of the seventeen patients who had fits these lasted more than 3 hours, and in four they were terminated only by death.

Vomiting was another constant symptom, and in most patients it was severe. Eleven patients vomited black or dark-brown material. It was notable that vomiting invariably ceased or became much less frequent shortly after admission, that is, a few hours after the onset of stupor or coma.

The respiratory rhythm was noted to be abnormal in twenty cases, and most exhibited changing patterns of breathing. Hyperpnœa and irregular respirations were the commonest abnormalities noted, but shallow or rapid breathing also occurred, and one patient, who became apnœic, remained alive for 26 hours with assisted respiration.

The liver was palpable in twelve, and in seven it seemed, on repeated examination, to have become larger than on admission. In six the liver was thought to be abnormally firm, and this was, in our experience, a more helpful finding than apparent enlargement.

Muscle-tone and tendon-reflexes tended to be changeable. Increased or variable tone and tendon-reflexes were found in sixteen. The plantar responses were abnormal or equivocal in about half of the group, and they were often variable from time to time in the same patient. The pupils became dilated or unresponsive to light, or both, in ten patients. In only one patient were the pupils unequal.

A characteristic posture was observed—the elbows flexed, the legs extended, and the hands clenched—and some or all of these features were noted in seven patients. This finding, in common with hyperpnœa, firmness or enlargement of the liver, and changes in the muscle-tone and tendon-reflexes, was more often recorded in the more recently admitted cases, when clinicians at the hospital had become familiar with the condition.

In twelve patients ketones were found on urine analysis, or there was a ketonic odour on the breath. Every patient except one had fever while in hospital, but this was not

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‡ These may be had from *The Lancet*, 7, Adam Street, Adelphi, London, W.C.2.

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# DEGENERATIVE CHANGES IN THE AORTA OF SHEEP INJECTED WITH ONE MILLION UNITS OF VITAMIN $D_3$

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By

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## INTRODUCTION

In 1962 we examined histologically several organs from each animal in a small group of adult Blackface ewes which had received a single intramuscular injection of one million units vitamin $D_3$ in 2 ml. ethyl oleate approximately eleven months before slaughter. These sheep had been used in an experimental study of blood levels of vitamin $D_3$ after its injection (Quarterman, Dalgarno and Adam, 1964). The histological studies were made to investigate possible pathological effects of the treatment, and tissues from twelve normal Blackface ewes that were believed to have had no more than ordinary amounts of dietary vitamin D were used as controls.

All the animals in both groups had small calculi in the renal pelvis. Non-calcified arteriosclerotic intimal lesions were found in the aorta of two of the treated sheep. The remaining five had a mild, diffuse, medial fibrosis of the aortic wall.

We supposed that the arteriosclerotic lesions were due to vitamin D toxicity. Whilst it appeared unlikely that such lesions would have shortened the useful life of the sheep or have other economic disadvantages, we felt obliged to make a similar study on a larger group of animals in order to check this observation.

## MATERIALS AND METHODS

Forty Blackface ewe hoggs, with no history of disease, were bought from a reputable source when one year old. They were born in Strathdon, Aberdeenshire, kept on hill grazing during the summer, and on lowland grazing supplemented with turnips and hay in winter. They had not been injected with vitamin D or with prophylactic vaccines.

The animals were weighed, ear-marked, divided into groups and injected with vitamin $D_3$ on 25.5.62 as shown in Table 1. After injection the sheep were kept on grass for a short time until sheared, when they were transferred to marginal hill grazing until the end of September. Early in October they were returned to grass, receiving silage from 28.12.62 to 8.1.63, hay and ¼ lb. concentrates from 8.1.63 to 5.2.63.

Immediately after slaughter the heart, thoracic aorta and pieces of lung were placed in neutral buffered 4 per cent. formaldehyde solution. After about two hours the heart was freed from blood clots and adventitious tissue, examined and weighed. Tissues for further fixation and processing for histological examination were then selected from each chamber of the heart, from similar areas of the aortic arch and from the lung. Three specimens were taken from each aorta.

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Paraffin wax sections from each specimen obtained at two and four months after the injections were stained by the von Kossa method for calcium salts. Sections from all specimens were stained by van Gieson's picro-fuchsin method for collagen and by the Weigert-Sheridan method for elastic tissue. In addition, selected tissues were stained by the Periodic-acid-Schiff and haemalum method, by Heidenhain's iron haematoxylin method for the study of smooth muscle cells and by the silver impregnation of reticular fibres. Frozen sections were stained by Sudan IV.

## RESULTS

The treated and control groups did not show a significant difference in average carcase weights. Neither macroscopic nor microscopic lesions were found in the heart or lung of any animal, except for parasitic lung lesions. The heart weights from the three groups were not significantly different. The von Kossa preparations were all negative for calcium salts. Although no changes were seen with the unaided eye microscopic lesions were present in many of the sections of aorta and were classified as localised or diffuse. The former were found in animals from all three groups and were apparently unrelated to the treatment, whereas the latter occurred in all the animals injected with 1,000,000 units vitamin $D_3$ and we believe were attributable to this cause.

TABLE I

| Group | No. of ewes | Intramuscular injection | Slaughter: time after injection | | | |
|---|---|---|---|---|---|---|
| | | | 2 months | 4 months | 6 months | 8 months |
| 1 | 16 | 1,000,000 units vitamin $D_3$ dissolved in 2 ml. ethyl oleate (Robert Young & Co. Ltd.) | 4 | 4 | 4 | 4 |
| 2 | 8 | 500,000 units vitamin $D_3$ in 1 ml. ethyl oleate | — | 4 | — | 4 |
| 3 | 16 | 2 ml. ethyl oleate | 4 | 4 | 4 | 4 |

### *Spontaneous Arteriosclerotic Lesions occurring in Treated and Untreated Animals*

The non-specific changes were localised arteriosclerotic lesions. These occurred as intimal scars and plaque-like elevations of the intima.

*Intimal scars.* Of the sixteen animals injected with 1,000,000 units vitamin $D_3$, seven had one or more small sub-endothelial scars in the aorta. In two of the seven affected animals multiple lesions were found. Three out of eight receiving half the above dose showed similar areas of fibrosis.

In five of the sixteen controls there were lesions similar to those in the treated groups. The typical appearance of these arterio-

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sclerotic areas is shown in Fig. 1. Calcified, atheromatous or active inflammatory lesions were not found.

*Intimal plaques in the aorta.* In four of the treated ewes and three of the controls there were intimal plaques in the aorta (Fig. 2). These plaques consisted of smooth muscle cells, elastic fibres and collagen. They were covered with endothelium and did not contain demonstrable fat. They were superficial to the inner elastic layers of the vessel wall and appeared to be localised thickenings of the subendothelial tissues.

*Diffuse Lesions in the Aorta occurring only in Animals Injected with Vitamin $D_3$*

Staining for elastic tissue, collagen and reticulum showed a variable but generally slight increase in these tissues in the aortic media in the region of the larger smooth muscle bundles at six and eight months after the injection of 1,000,000 units vitamin $D_3$. In the same specimens, but not in the controls, there was a diffuse, patchy degeneration and atrophy of smooth muscle. This diffuse muscular lesion was present at two months after the injection, when vacuolar degenerative changes were present; these became progressively worse up to six months and at eight months the main appearance was of mild, diffuse atrophy of smooth muscle (Figs. 3 to 8). In some of the affected areas there was a considerable increase in fine elastic fibrils (Fig. 9). The wall of the aorta was slightly oedematous in these specimens, but fatty change was not present.

There were also lesions in the vasa vasorum of the aorta. These were infrequent and consisted of swelling or proliferation of vascular endothelium sufficient to reduce effectively the vessel lumen (Fig. 10). This change appeared to be confined to the group injected with 1,000,000 units vitamin $D_3$; only half of the sheep in this group were found to be affected and in them we were unable to find more than one or two occluded vessels per animal. There was no direct evidence of medial ischaemia even in areas of smooth muscle which showed relatively marked degenerative changes. There was no significant perivascular fibrosis in comparison with the control specimens.

## DISCUSSION

It is possible that the "spontaneous" aortic scars and plaques were caused by ethyl oleate, the vitamin injection vehicle. Our data do not resolve this question, but since intimal plaques in the aorta have been noted incidentally in other species it seems probable that they are non-specific.

Spontaneous, non-atheromatous, arteriosclerotic lesions in the aorta are fairly common in captive wild mammals (Fox, 1933, 1939; Ratcliffe and Cronin, 1958; Lloyd, 1959; Ratcliffe, Yerasimides and Elliott, 1960; Finlayson, Symons and T-W-Fiennes, 1962). Similar lesions have been recorded in several domesticated species (Fox, 1933). Gottlieb and Lalich (1954) examined more than 2,000 fresh

aortas from pigs slaughtered in American abattoirs. Arteriosclerotic lesions were found in all age-groups, reaching an incidence of 35 per cent. in pigs over 3 years old. Principally the lesions were fibrous thickenings of the intima. In one middle-aged pig, Jennings, Florey, Stehbens and French (1961) found plaque-like intimal lesions, superficial to the internal elastic lamina of the aorta. These plaques were relatively acellular, but contained intra- and extracellular fat and areas of calcification. Non-fatty, fibrous intimal plaques in the thoracic aorta have been recorded in the cat (Lindsay and Chaikoff, 1955) and in the dog (Lindsay, Chaikoff and Gilmore, 1952), but the rat appears to be relatively free from spontaneous vascular disease (Wilens and Sproul, 1938) except in repeatedly bred animals, where spontaneous arteriosclerotic lesions commonly occur in the main arteries of both sexes (Wexler, 1964). Wexler found that the lesions were more common and more severe in the female; 40 per cent. of a large group showed grossly detectable lesions and 80 to 90 per cent. had microscopic lesions. In the course of other investigations, Hulland (1960) observed a high incidence of arterial changes in the visceral arteries of both normal and diseased sheep. Sudanophilic areas were found in the aortic intima in some cases, but the incidence of arteriosclerotic changes in this organ was not recorded. Lesions of the media were not common in any vessel.

Generally, these spontaneous intimal lesions in younger mammals resemble those which we found in sheep in this experiment, being mainly fibrous thickenings of the intimal tissues, containing elastic fibres and occasionally some smooth muscle cells, but rarely lipid. In older animals and particularly in the aging pig, there is a tendency to atherosclerosis (French, Jennings, Poole, Robinson and Florey, 1963). The aetiology of the condition is obscure.

We believe the diffuse changes in the arterial wall to be genuine pathological effects of the treatment. The actual cause of these microscopic degenerative lesions in smooth muscle is not clear. Presumably the vasa vasorum play an essential part in supplying the outer parts of the arterial wall with nutrients and it seems probable that atrophy of smooth muscle could be a consequence of an interrupted local blood supply. It is unlikely, however, that the few abnormal vasa vasorum which we were able to find could cause a serious circulatory deficiency. On the other hand, these could be the residue of a more widespread vascular lesion such as the arteritis described by Gillman and Gilbert (1956) and Hass, Trueheart, Taylor and Stumpe (1958) in vitamin D intoxication. If so, it is surprising that the coronary arteries and myocardium escaped injury.

Alternatively, the changes in aortic smooth muscle could possibly be the sequel to a direct injury sustained soon after the vitamin injection. Gross calcification probably did not occur, since such deposits tend to be relatively persistent in the aorta and cause distinct focal scarring of the media (Gillman, Grant and Hathorn, 1960; Quarterman, Dalgarno, Adam, Fell and Boyne, 1964). It should be

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noted, however, that the aorta can accumulate considerable amounts of calcium before mineralisation can be detected by routine histochemical procedures (Gillman and Gilbert, 1957).

Finally, the medial degenerative change could possibly have some relationship to the lesions of skeletal muscle observed by Gillman and Gilbert (1957) in rats suffering from vitamin D poisoning. In this case the skeletal muscle underwent atrophy and extensive degeneration with dissolution, due possibly to a direct toxic action of the vitamin. On the other hand, similar changes found in rabbits given very high levels of Vitamin D were thought to be due to arteritis (Hass *et al.*, 1958).

## CONCLUSIONS

A single intramuscular injection of one million units vitamin $D_3$ in normal sheep resulted in degeneration of the smooth muscle of the aortic media. No histological lesions due to this treatment were detected in the heart or lung. The pathogenesis of the lesion is not understood; damage to the vasa vasorum of the aorta or direct toxic action of vitamin D are suggested as possible causes. Both the injected and control animals showed a high incidence of spontaneous intimal arteriosclerotic lesions.

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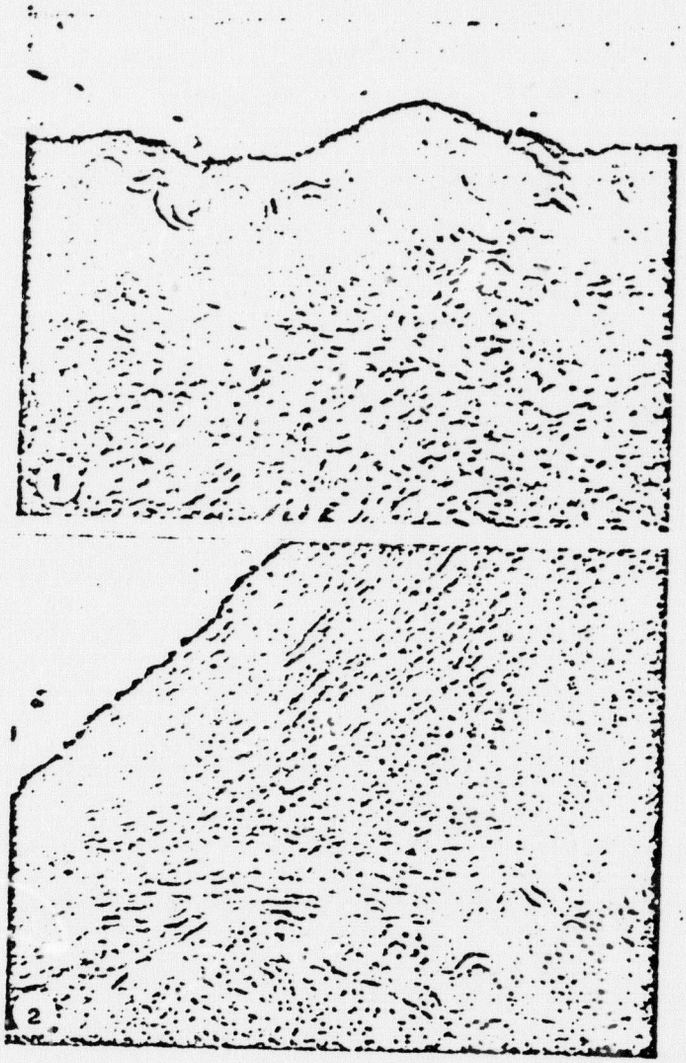

Fig. 1. Spontaneous sub-endothelial scar in the aorta of a control sheep. Van Gieson, × 150.

Fig. 2. Fibrous plaque in the aorta of a control sheep. Van Gieson × 150.

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# The Syndrome of Supravalvular Aortic Stenosis, Peripheral Pulmonary Stenosis, Mental Retardation and Similar Facial Appearance*

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IN A previous communication we reported about the findings on patients with supravalvular aortic stenosis in association with mental retardation and a certain facial appearance.[1] Prior to this report, Williams and co-workers[2] drew attention to this combination of defects. The authors suggested that the presence of supravalvular aortic stenosis in mentally retarded patients with the same unusual facial features might constitute a previously unrecognized syndrome. It is well known that at least three different anatomic conditions may cause supravalvular aortic obstruction and that this type of aortic stenosis may be associated with some degree of generalized hypoplasia of the entire aorta distal to the stenosis or with an aorta of normal caliber. Since in the cases of supravalvular aortic stenosis reported in the literature prior to the report of Williams and co-workers,[2] additional mental retardation and the striking similarity of the facial appearance was apparently not present, the question remained whether this combination of lesions occurs only in a particular type of supravalvular aortic stenosis. Meanwhile, we have seen more patients with this condition, and our series consists now of 11 patients, 10 of these with the above-mentioned combination of lesions. Further observations on these patients, particularly the finding of coexistent multiple peripheral pulmonary stenosis and identical dental malformations, are the basis of the present report.

## CLINICAL FEATURES

### GENERAL APPEARANCE

Table 1 summarizes the clinical data of 10 patients with supravalvular aortic stenosis. Patients 1, 2 and 3 have already been described in our first communication about this subject.[1] One additional patient not included in Table 1 had a different type of supravalvular aortic stenosis, characterized by a uniform narrowing of the entire ascending aorta.[3] This patient will be discussed separately below. The 10 patients listed in Table 1 have localized narrowing of the ascending aorta just above the sinus of Valsalva; they are mentally retarded and have the same characteristic facial appearance. Figure 1 shows photographs of nine of these patients and Figure 2 is the photograph of the tenth patient. These 10 patients were between 2 and 14 years of age when first seen in this clinic. There are 8 girls and only 2 boys in this series. The diagnosis of supravalvular aortic stenosis was confirmed at operation in 5 of them.† All have been preoperatively diagnosed as having supravalvular aortic stenosis. This was clearly demonstrated by transseptal left heart angiocardiography. Intelligence quotients, determined in 8 patients, ranged from 44 to 80

† Operated on by Dr. J. Koncz, Department of Thoracic Surgery, University of Göttingen.

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TABLE 1
Clinical Data of 10 Patients

| No. & Sex | Age (yr.) | Diagnosis Confirmed | I.Q. (%) | Facies & Dental Anomalies | Periph. Pul. Sten. | Age at Onset Symptoms (yr.) | Exercise Tolerance | Murmur, Thrill |
|---|---|---|---|---|---|---|---|---|
| 1 M | 7 1/2 | Operation | 46 | Typical; + | + | 3 | Reduced | Systolic, most pronounced in 1st right intercostal space |
| 2 M | 7 1/2 | Operation | 46 | Typical; + | ? | 2 | Reduced | Systolic, most pronounced in 1st right intercostal space |
| 3 F | 10 | Operation | 58 | Typical; + | + | 3 | Reduced | Systolic, most pronounced in 1st right intercostal space |
| 4 F | 8 | Operation | 80 | Typical; + | ? | 6 | Reduced | Systolic, equally pronounced in 1st and 2nd rt. intercostal space |
| 5 F | 6 | Operation, autopsy | * | Typical; + | + | 4 | Reduced | Systolic, most pronounced in 2nd and 3rd right intercostal space |
| 6 F | 14 | Angiogram | 44 | Typical; + | ? | 5 | Reduced | Systolic, most pronounced in 2nd right intercostal space |
| 7 F | 3 1/2 | Angiogram | 57 | Typical; + | +++ | 2 1/2 | Reduced | Systolic, most pronounced in 2nd right intercostal space |
| 8 F | 3 | Angiogram | 58 | Typical; + | +++ | 2 1/2 | Reduced | Systolic, equally pronounced in 2nd left and right intercostal space |
| 9 F | 2 | Angiogram | 74 | Typical; + | + | None | Normal | Systolic, most pronounced in 2nd right intercostal space |
| 10 F | 3 | Angiogram | * | Typical; + | +++ | 2 | Reduced | Systolic, most pronounced in 2nd right intercostal space |

* Retarded but not tested.
Periph. Pul. Sten. = Peripheral Pulmonary Stenosis; Dim. = diminished.

(normal value: 100, Wechsler).* The 2 patients that were not tested are also mentally retarded.

*The facial characteristics* of these patients are as described previously.[1,2] There are distinct soft-tissue similarities, but the facial resemblance is partly determined by hypoplasia of the mandible. All have the same friendly temperament. They are very active and always happy. The similarity of appearance is even more striking when they talk, all with the same deep somewhat metallic voice. In total they are what one would describe as charming characters. Four of these 9 patients have strabismus convergens concomitans alternans (Case 1, 6, 7, and 9), and 1 has an epicanthus (Case 1). The retinal vessels are normal.

## DENTAL ANOMALIES

Nine of the 10 patients listed in Table 1 have had repeated examinations by a dental surgeon and orthodontist (Schulze). These examinations revealed specific and otherwise very rare anomalies. The dental malformations are more severe in the 2 boys than in the 8 girls. Therefore, they will be described separately.

*Boys:* In the *deciduous dentition* of Case 1 the lower lateral incisors ($\overline{II \mid II}$) are absent. Earlier roentgenograms revealed that there never was an anlage of these teeth. Case 2 has a complete deciduous dentition. However, most of the teeth of both these boys are extremely small and hypoplastic. In addition, the upper milk molars of both boys show deformities that have so far not been described. Both dorsal tooth-knobs (metaconum and hypoconum) are markedly reduced, causing a round crown instead of the usual rhomboidal form in $\underline{V \mid V}$. A decrease of the masticatory surface with consecutive convergence of the lateral tooth area results in peculiar bud-shaped teeth (Figure 3). There is no reduction in the number of knobs of the lower milk molars. However, here the masticatory surface is also smaller than normal with an abnormal convergence of the lateral tooth area, particularly on the buccal side.

*The permanent dentition* of both boys is also incomplete. In Case 1 there is no anlage of

* Tested by Dr. H. Schlange, Department of Pediatrics, University of Göttingen.

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TABLE 1 (*continued*)

| Second Aortic Sound | B.P. in Arms (mm. Hg) Right | Left | X-ray C-T Ratio | Electrocardiogram QRS Axis | LVH | LV Strain | RVH | Present Condition |
|---|---|---|---|---|---|---|---|---|
| Dim. | 135/75 | 110/85 | No aortic knob; empty pedicle. 45% | +86° | + | + | 0 | Improved postoperatively (operation Oct. 1962) |
| Dim. | 140/80 | 130/80 | No aortic knob; empty pedicle. 48% | +43° | + | + | 0 | Improved postoperatively (operation July 1962) |
| Dim. | 135/75 | 115/75 | No aortic knob; empty pedicle. 53% | +99° | LV preponderance | 0 | 0 | Improved postoperatively (operation April 1962) |
| Dim. | 100/80 | 100/80 | No aortic knob; empty pedicle. 44% | +57° | 0 | 0 | 0 | Improved postoperatively (operation Nov. 1962) |
| Equal to $P_2$ | 150/80 | 115/80 | No aortic knob; empty pedicle. 52% | +68° | + | + | 0 | Died at operation |
| Dim. | 130/80 | 115/75 | No aortic knob; empty pedicle. 46% | +82° | + | 0 | 0 | Operation scheduled |
| Dim.; $P_2$ loud | 105/70 | 100/70 | No aortic knob; empty pedicle. 52% | +95° | 0 | 0 | + | Operation scheduled |
| Dim.; $P_2$ loud | 115/80 | 130/80 | No aortic knob; empty pedicle. 54% | +98° | 0 | 0 | + | Operation scheduled |
| Dim. | 120/80 | 120/80 | No aortic knob; empty pedicle. 53% | +65° | 0 | 0 | 0 | Operation scheduled |
| Dim. | 110/90 | 130/95 | No aortic knob; empty pedicle. 50% | +96° | + | 0 | + | Operation scheduled |

$\overline{2}\,|\,\overline{2}$ and $\underline{5}\,|\,\underline{5}$ and in Case 2 no anlage of $\underline{5\,4}\,|\,\underline{5}$ and $\underline{5}|$. All incisors are smaller than normal. The sum of the four upper incisors of Patient 2 amounts to 25 mm. instead of 32 mm., the average for these teeth. The first lower molars are also malformed. Their disto-lingual knobs (entoconid) are hypoplastic. The roots of these teeth are very short and thin.

In addition to these abnormalities in number, shape and size of the deciduous and the permanent teeth, there is a marked *dysgnathism*. The upper dental arch is too broad, whereas the lower is too small. Consequently, the upper arch overlaps the lower at the end of the mastication. Therefore, the act of chewing is severely disturbed (Fig. 4).

*Girls:* The girls have less pronounced dental malformations, but deformities of the incisors and hypoplasia of the teeth of the same kind are also present (Fig. 5). The sum of the upper incisors of Patients 4 and 6 amounts only to 26 and 27 mm., respectively, if in patient 6 one counts $|\underline{2}$ twice, because $\underline{2}|$ is lacking. All of these girls have the typical reduction in size and shape of their teeth as seen in the boys. Partial anodontia and a delayed mineralization of some teeth are also an expression of the same maldevelopment of the dental anlage.

### CHROMOSOME STUDIES

Three of the patients (Cases 1, 3 and 6) had chromosome studies. Leucocytes of peripheral blood were cultured according to the method of Moorhead and co-workers[4] for three to four days. During the last four to seven hours of the cultures, colchicine was added and the microscopic preparations were stained with Unna[5] or acetoorcein. A total of 50 metaphase-plates from each patient have been studied microscopically, and photographs were taken to count the chromosomes. In oral smears, resting nuclei were scanned for Barr bodies (P. Eberle). In all patients the chromosome number is 46, and no chromosome seemed to be abnormal in structure and length. Outstanding in the karyotype analysis was the observation that the male patient (Case 1), who has no descensus testiculorum, had an abnormal y-chromosome. This y-chromosome appeared to be somewhat short, making it difficult to differentiate it

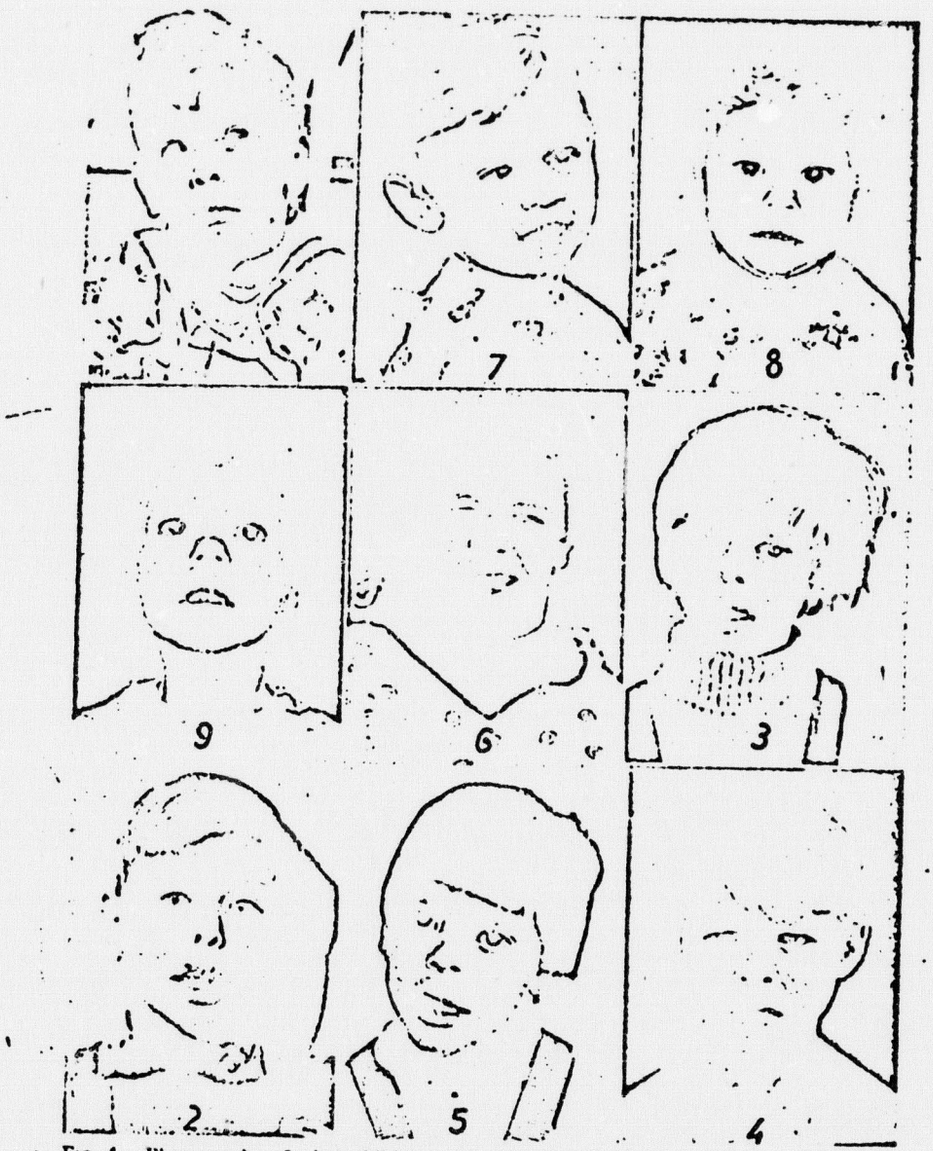


FIG. 1. Photographs of nine children with supravalvular aortic stenosis. Numbers correspond to case numbers in Tables I and II. (Figures 1, 3 and 5 from *Circulation*, 26: 1235, 1962, reproduced by permission from the American Heart Association.)

from the chromosomes of Case 21. However, we do not believe that this is of significance in regard to the syndrome of supravalvular aortic stenosis.

### CARDIAC SYMPTOMS AND FINDINGS

The clinical symptoms of these patients have been described earlier;[1,2] they are not different from those of patients with other types of aortic stenosis. The exercise tolerance was reduced in 9 of the 10 patients. The systolic murmur and thrill were most pronounced in the first right intercostal space in 3 of the patients, and there was no difference in the intensity of the murmur in the first and second right intercostal spaces in 1 patient. In the others it was loudest in the second right intercostal space. The second sound in the aortic area was diminished in all but 1 patient. There were significant blood pressure differences at

FIG. 2. Photograph of patient 10.

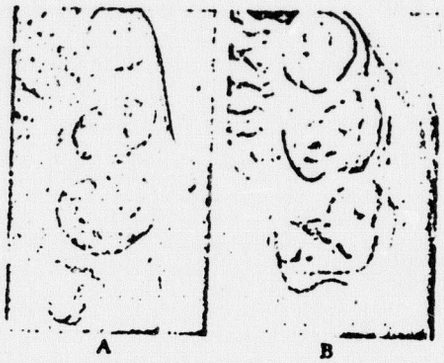


FIG. 3. A, teeth of Patient 1. Bud-shaped $\overline{V}$ and hypoplasia of the dorsal knobs. B, normal milk molars of a healthy child of the same age.

the upper extremities in 7 of the 10 patients. The hearts were only slightly to moderately enlarged on roentgenograms, the C-T ratio ranging from 44 to 54 per cent. The roentgenograms of the hearts of the patients with supravalvular aortic stenosis were characterized

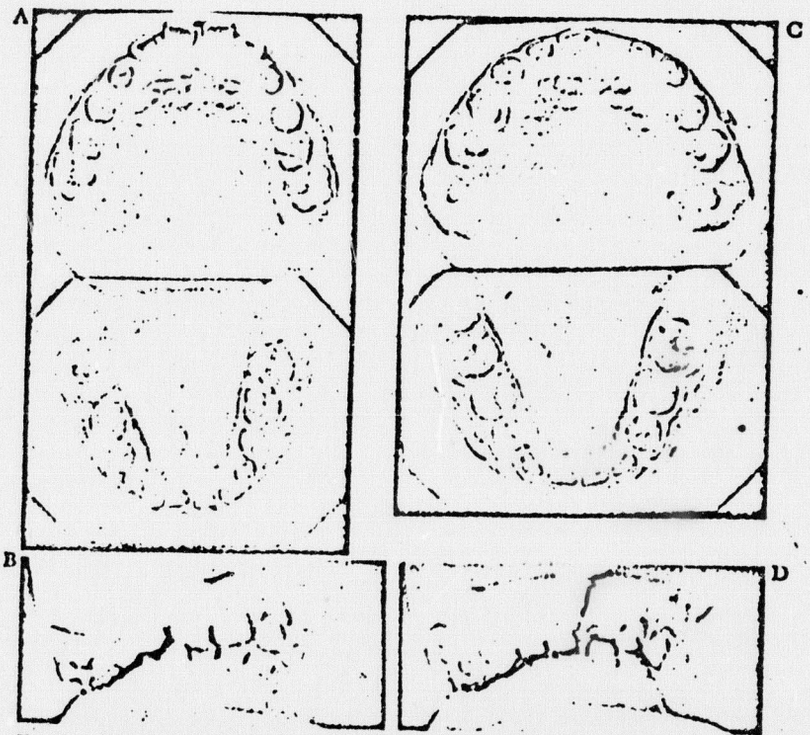


FIG. 4. A, Case 2. Impressions of maxilla and mandible shows microdontism. The maxilla is too broad, the mandible too small. B, Case 2. Vestibulo-occlusion of the upper lateral teeth. Mastication is severely disturbed. C, Case 1. Malformed and hypoplastic teeth. The maxilla is too broad, the mandible too small. D, Case 1. The maxilla overlaps the mandible at the end of mastication. There is no chewing contact of antagonists.

FIG. 5. Case 6. Dental impressions.

by the absence of the aortic knob and a somewhat empty vascular pedicle in which no shadow of the aorta could be seen. The electrocardiograms of only 4 patients showed marked left ventricular hypertrophy, and in three electrocardiograms there was left ventricular strain.

CARDIAC CATHETERIZATION DATA

In 8 of the 10 patients (Table II), the left ventricle was entered, and there was a significant systolic gradient between the left ventricle and ascending aorta. The left atrium was catheterized in all of these patients, and there was in no instance significant mitral regurgitation. There was also no evidence of any other additional intracardiac malformations.

*Right Ventricular Angiocardiography:* Surprisingly, the right ventricular and pulmonary artery pressure was elevated in 7 of these patients (Cases 1, 3, 5, 7, 8, 9 and 10). There was no gradient between the right ventricular and pulmonary artery pressure of these seven. At least in four instances the marked elevation of the pulmonary artery pressure could not be explained on the basis of supravalvular aortic stenosis. Therefore, selective right ventricular

TABLE II

Catheterization Data and Selective Angiocardiography of 10 Patients.

| No. & Sex | Pressures (mm. Hg) | | | | | Angiocardiography | | |
|---|---|---|---|---|---|---|---|---|
| | LV | LV-Aortic Syst. Gradient | LA-Mean | RV | PA | Ventricular Septum | Left Heart | Right Heart |
| 1 M | 165/0 | 50 | 6 | 40/0 Symmetrical pointed tracing | 42/15 | Intact (dye-$N_2O$) | Supravalvular aortic stenosis | Bilateral, multiple peripheral pulmonary stenosis |
| 2 M | 165/0 | 65 | 7 | 32/0 | 29/8 | Intact ($N_2O$) | Supravalvular aortic stenosis. Collaterals between coronaries and mediastinal vessels | Not done |
| 3 F | 230/0 | 120 | 5 | 55/0 | 55/12 | Intact | Supravalvular aortic stenosis | Bilateral, multiple peripheral pulmonary stenosis |
| 4 F | 130/0 | 30 | 5 | 35/0 | 26/7 | Intact | Supravalvular aortic stenosis | Not done |
| 5 F | 165/0 | 65 | 7 | 46/0 Symmetrical pointed tracing | 37/11 | Intact | Supravalvular aortic stenosis | Bilateral, multiple peripheral pulmonary stenosis |
| 6 F | 190/0 | 90 | 5 | 32/0 | 26/6 | Intact (dye) | Supravalvular aortic stenosis | Not done |
| 7 F | 160/8 | 55 | 4.5 | 95/0 Symmetrical pointed tracing | 95/20 | Intact | Supravalvular aortic stenosis | Bilateral, multiple peripheral, pulmonary stenosis, severe |
| 8 F | 120/0 | 20 | 4 | 110/0 Symmetrical pointed tracing | 110/40 | Intact | Supravalvular aortic stenosis | Bilateral, multiple peripheral pulmonary stenosis, severe |
| 9 F | Not entered | Undetermined | 4 | 44/0 Symmetrical pointed tracing | 32/6 | Intact | Supravalvular aortic stenosis | Bilateral, multiple peripheral, pulmonary stenosis |
| 10 F | Not entered | Undetermined | 8 | 75/0 | 70/10; peripheral 20/5 | Intact | Supravalvular aortic stenosis | Bilateral, multiple peripheral pulmonary stenosis, severe |

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FIG. 6. Case 8. Pulmonary angiocardiogram shows multiple, peripheral stenosis in both pulmonary arteries. Pulmonary artery pressure was 110/40 mm. Hg.

FIG. 7. Case 7. Right ventricular angiocardiogram showing multiple, peripheral stenosis in both pulmonary arteries. Pulmonary artery pressure 95/20 mm. Hg.

angiocardiography was performed in addition to left ventricular angiocardiography. This demonstrated severe, multiple peripheral pulmonary stenoses of both lungs in four patients (Cases 3, 7, 8 and 10). Their pulmonary artery pressures were 55/12, 95/20, 110/40 and 70/10 mm. Hg, respectively. In the right ventricular angiocardiograms of the 3 other patients (Cases 1, 5 and 9) multiple, bilateral narrowing of the pulmonary arterial tree was also present but was hemodynamically less significant (pulmonary artery pressures 42/15, 37/11 and 32/6 mm. Hg, respectively). The 3 remaining patients have not had right heart angiocardiography. Figures 6 and 7 show the peripheral pulmonary stenoses of Patients 7 and 8, and Figure 8 is the electrocardiogram of one of these two patients showing right ventricular hypertrophy.

*Left Heart Angiocardiography:* This demonstrated a localized narrowing of the aorta immediately above the sinus of Valsalva in all patients (Fig. 9 and 10). Distal to the stenotic area the ascending aorta resumed an almost normal caliber in most of them. In some, the aorta, although it showed a distinct supravalvular stenotic area, did not resume a normal caliber distal to the stenosis but remained markedly hypoplastic throughout its course. There was a marked bulging of the aorta at the site of the obliterated ductus arteriosus in all of these patients.

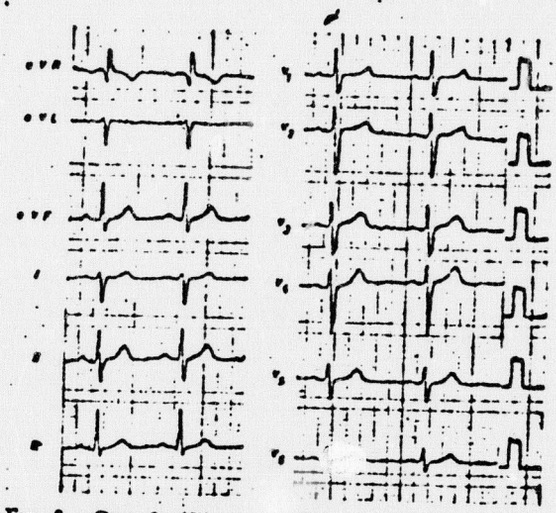

FIG. 8. Case 8. Electrocardiogram shows right ventricular hypertrophy in patient with severe peripheral pulmonary stenosis.

## SURGICAL FINDINGS

At operation of the first 5 children an almost circumferential crista with a fibrotic thickening of the inner wall of the aorta was found. This was most pronounced above and between the ventral and the left aortic leaflet. In Case 3 there was a waistlike uniform narrowing, and in Case 2 the ventral and the left aortic leaflets were fused with the stenotic area, thus covering the orifice of the left coronary artery. A detailed report about the operations will be prepared by Dr. J. Koncz, who operated on these children.

The eleventh patient of this series, a 10 year old boy, is not included in Table 1; his findings have already been published.[8] He had a normal facial appearance, was not mentally

FIG. 9. Case 7. Left ventricular angiocardiogram following transseptal left heart catheterization. a, P-A view shows supravalvular aortic stenosis. Marked bulging of aorta at the site of the ligamentum arteriosus can be seen in all patients with this syndrome. b, lateral view shows stenosis above the sinus of Valsalva.

retarded and his supravalvular aortic stenosis was distinctly different. There was a uniform narrowing of the entire ascending aorta, extending high up into the aortic arch and behind the origin of the large arterial vessels.

## Discussion

Different anatomic conditions may cause supravalvular aortic stenosis. An increasing number of patients with this condition has now been reported, preoperatively diagnosed and operated upon.[6-17] In most of the earlier reported cases there was a fibrous band crossing the aortic lumen but causing apparently no obstruction to left ventricular outflow.[18-22] Functionally significant narrowing of the ascending aorta at the upper margin of the sinus of Valsalva is caused by a localized narrowing of this part of the aorta, with or without a circumferential crista or a membranous structure which contributes to the narrowing of the aortic lumen. There is usually marked plication of the inner wall of the aorta. As Morrow and associates[6] have pointed out, one or more leaflets of the aortic valve may be fused to the thickened wall of the stenotic part of the aorta, thus covering the respective coronary orifice to some extent. From experience with autopsy specimens of this type of congenital malformation, Lev[23] has reported that supravalvular aortic stenosis may occur as an isolated lesion and as part of generalized hypoplasia of the entire aorta. Some of our patients have significant hypoplasia of the aorta distal to the stenosis. There is one more anatomic variant of supravalvular aortic stenosis which is apparently even less frequent than the usual types. It is a uniform narrowing of the ascending aorta beginning also at the upper margin of the sinus of Valsalva but extending high up into the aortic arch, the origin of the great arteries at the aortic arch being within the stenotic area. This form is distinctly different from the usual supravalvular aortic stenosis and should be termed "unusually long supravalvular aortic stenosis." We have reported such a case[8] in detail, and Neufeld and associates[24] also published studies on a case of this kind of hypoplastic aorta.

*The exact diagnosis of supravalvular aortic stenosis* can best be established by left ventricular injection of contrast medium and biplane angiocardiography. Besides the facial similarity, there are no specific signs which would

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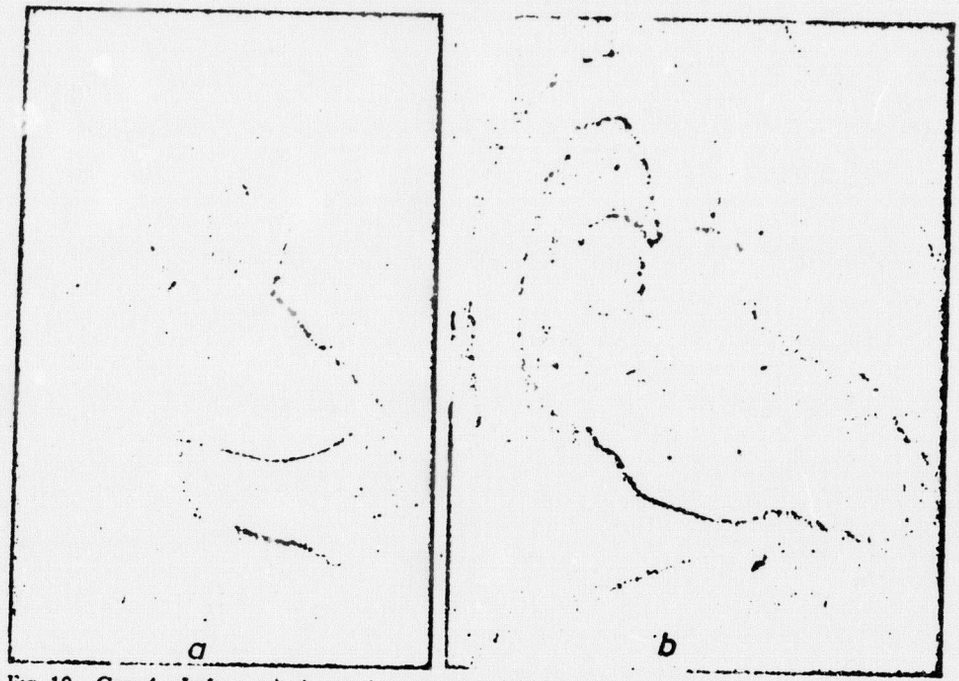


FIG. 10. Case 4. Left ventricular angiocardiogram following transseptal left heart catheterization. a, P-A view showing intact aortic valve and supravalvular aortic stenosis above the sinus of Valsalva. b, lateral view shows supravalvular stenosis and bulging of the aorta at the site of the ligamentum arteriosus.

permit the differentiation of supravalvular aortic stenosis from other types of aortic stenosis on physical examination. In some cases the thrill and the systolic murmur may be most pronounced higher up in the right precordium just below the clavicle. The second aortic sound was diminished in all our cases. Of interest is the frequent finding of different blood pressures in both arms, as reported also by others, and it may help in the differentiation. The roentgenogram of the heart may, however, offer a diagnostic clue. The emptiness of the vascular pedicle and the fact that no aortic knob can be seen should make one suspicious of this type of aortic stenosis.

It is a striking and most surprising fact that we have seen within one and a half years 10 of these patients with the facial characteristics described previously,[1,2] with mental retardation and with certain similarities in temperament and nature. We do not believe that there is any external reason for the sudden occurrence of this malformation such as the thalidomide malformations seen in this country. The relatively frequent recognition of this combination of lesions is probably due to the fact that in recent years more detailed studies, including left ventricular angiocardiography, have been performed as compared to some years ago.

It may be worthwhile to point out that we have been able to differentiate by left ventricular angiocardiography the fusion of the leaflets of the aortic valve with the stenotic wall of the aorta from the cases without such a fusion. The surgeon will see this anyway at operation, but this differentiation may throw some light upon the result of operation to be expected and the risk of operation.

The bulging of the aorta at the site of the ligamentum arteriosus, which can be seen in the left ventricular angiocardiograms of all of our patients with this syndrome, seems to be specific for this malformation. It may also be an expression of the maldevelopment of the aorta and the pulmonary artery.

*Peripheral Pulmonary Stenosis:* Besides the identical dental malformations of these patients, the most interesting new finding is the coexistence of multiple bilateral peripheral pulmonary stenosis in at least 7 of 10 patients with this syndrome. In 4 cases this was so severe in degree that it could not be missed: the pulmonary artery pressure was significantly elevated; there was no gradient across the

pulmonary valve; the cardiac catheter could not be advanced into a pulmonary wedge position because of the severe multiple narrowings in both pulmonary arteries. In the 3 other patients who had right heart angiocardiography, bilateral multiple peripheral pulmonary stenosis was well demonstrated but hemodynamically less significant. The remaining 3 patients did not yet have right heart angiocardiography. Multiple peripheral pulmonary stenosis to a more or less significant degree is to be expected in these patients.

Gupta and Wiggers[25] have shown that in coarctation of the aorta the lumen of the aorta must be reduced by 55 to 60 percent before left ventricular and aortic pressure rises. It is also well known that in aortic and pulmonary stenosis the orifice of the valve must be narrowed considerably before the pressure proximal to the stenosis will be significantly elevated. Riley and co-workers,[26] in their classic paper on the hemodynamics of the pulmonary circulation, have demonstrated that the pulmonary circulation has a large reserve capacity. Therefore, peripheral pulmonary stenosis must be present to a considerable degree before pressure at rest rises in the main pulmonary artery. Dean and co-workers[24] have pointed out that in multiple peripheral pulmonary stenosis the pressure tracing from the main pulmonary artery proximal to the stenosis has a characteristic contour with a low diastolic pressure and a slow rate of ascent. Our 4 patients with marked elevation of the pulmonary artery pressure also had a low diastolic pressure, but in contrast to the finding of Dean and co-workers,[27] there was a steep ascent in the pressure tracing of the main pulmonary artery. The pressure tracing of the right ventricle exhibited the features of an isometric curve giving a symmetric, pointed tracing, similar to that of patients with pure pulmonic stenosis. Wiggers[28] has also commented on the decline of the diastolic pressure proximal to a coarctation of the aorta. According to Wiggers,[28,29] this is the result of reduced capacity of the aortic compression chamber and its increased volume elasticity coefficient. If such a compression chamber with a reduced distensibility receives a normal stroke volume, the systolic pressure rises and the diastolic pressure decreases.[28] The situation is similar in peripheral pulmonary stenosis.

Since Söndergaard[30] called attention to the clinical significance of postvalvular pulmonary stenosis in 1954, several cases, have been reported.[31–39] However, the total number of patients diagnosed as having this malformation is still small. It has been diagnosed only since the introduction of selective angiocardiography.[31] The terms "coarctation of the pulmonary artery," "postvalvular stenosis of the pulmonary artery," "supravalvular pulmonary artery stenosis" and "peripheral pulmonary stenosis" have been used to designate these lesions. Peripheral pulmonary stenosis may occur as an isolated lesion, or it may be associated with other cardiac defects. It may be a single stenosis or it may occur at multiple sites of the pulmonary arterial tree. In a high percentage of the cases reported in the literature the main pulmonary artery pressure was normal or only slightly elevated. Williams and co-workers[36] discussed this phenomenon in detail and pointed out that there are certain pitfalls in the diagnosis if it is based on catheterization findings alone. As may any congenital malformation, peripheral pulmonary stenosis may vary widely in its degree of severity.[36] Its presence in all of the patients of this series who have had right heart angiocardiography is highly significant. The etiology of supravalvular aortic stenosis and multiple supravalvular pulmonary stenosis, occurring in the same patient, is probably closely related.

*Combined Aortic and Pulmonic Supravalvular Stenosis:* Only a few cases of combined aortic and pulmonic stenosis have been reported.[40–42] These cases may present some diagnostic difficulties, since the clinical picture may be dominated by one of the two lesions. The electrocardiogram of such patients may show right ventricular hypertrophy and only minor signs of left ventricular hypertrophy, or predominant left ventricular hypertrophy. Only combined left and right heart catheterization and angiocardiography clear the situation. The coexistence of hemodynamically significant multiple peripheral pulmonary stenosis in cases of supravalvular aortic stenosis is of importance for the surgical management of these patients, since multiple peripheral pulmonary stenosis is inoperable and may cause considerable difficulties in the postoperative period following correction of supravalvular aortic stenosis.

*Dental Characteristics:* The outstanding and most frequent dental malformation is the reduction in size and the general hypoplasia of most of the teeth. Particularly the upper middle incisors are involved. Not only their size is abnormal but also their form. The

boys have additional malformations of the deciduous molars (bud-shaped). This seems to be specific. Partial anodontia and late mineralization of several teeth are closely associated with the reduction in size and form of the teeth. This is a heteromorphous expression of the degeneration of the anlage which also causes the general dental hypoplasia. Some of these dental malformations of the children with supravalvular aortic stenosis are extremely rare among other children. Therefore, the high percentage of its occurrence in these patients cannot be an incidental finding. These children also have hypoplasia of the mandible; the horizontal branch is too short as compared to the vertical branch, and the mandibular angle is larger than normal. This is partly responsible for the peculiar facial appearance of these children. Unusual dysgnathism is present only in the boys. They have expansion of the maxilla and compression of the mandibule that result in severe nonocclusion of the teeth.

*Pathogenesis of the Syndrome:* The association of mental retardation with the close facial resemblance of these children and the presence of clinical signs of aortic stenosis has led to the correct diagnosis of supravalvular aortic stenosis in the 4 patients of Williams and co-workers[2] and in our patients.[1] At that time it was suggested that we were dealing with a previously unrecognized syndrome, but there remained some doubt because several patients had been reported in the literature who had supravalvular aortic stenosis but a normal facial appearance and a normal mental capacity. After seeing the additional patients described in the present report and after the recognition of otherwise unknown or very rare identical dental malformations and multiple peripheral pulmonary stenoses, we have no doubt that this is a syndrome. It still needs to be explained why there are patients with supravalvular aortic stenosis without mental retardation and the peculiar facial appearance and probably also without additional peripheral pulmonary stenosis. The type of supravalvular aortic stenosis present in our eleventh patient, who had uniform narrowing of the entire ascending aorta, certainly does not belong to this syndrome.

The presence of peripheral stenosis in both great vessels points toward the possibility that defective formation of the aortic septum is responsible for the tendency of generalized hypoplasia and localized narrowing of the aorta and of the pulmonary artery. This is a disease with hypoplasia of several organs, particularly of both great vessels, the teeth and the mandible, and probably also of the cerebrum.

According to our observations on this subject, the syndrome consists of supravalvular aortic stenosis, multiple peripheral pulmonary stenosis, mental retardation with a characteristic facial appearance, otherwise rarely occurring complex dental malformations and with the frequent association of strabismus convergens concomitans.

## Summary

A series of 10 patients with supravalvular aortic stenosis and a similar facial appearance with mental retardation is described. The patients have identical dental malformations in addition, and 7 patients examined by right heart angiocardiography have multiple, bilateral peripheral pulmonary stenosis. Peripheral pulmonary stenosis is also expected to be present in the remaining patients. The clinical features and the findings obtained at cardiac catheterization, angiocardiography and operation are discussed. Chromosome studies on 3 of these patients have been negative. It is suggested that defective formation of the aortic septum is responsible for the coexistence of peripheral stenosis in both great vessels. The malformation is characterized by hypoplasia of several organs.

The findings represent a new syndrome: supravalvular aortic stenosis, peripheral pulmonary stenosis, mental retardation, a certain facial appearance and complex dental malformations.

## Addendum

Meanwhile, right heart angiocardiography has been performed in Patients 2, 4 and 6. Multiple peripheral pulmonary stenoses are also present in these patients. Since the submission of this paper, it has been suggested[3, 4] that the patients with supravalvular aortic stenosis and the characteristic facial appearance represent the survivors of the syndrome of infantile hypercalcemia. Recently we have examined 2 additional children with the same combination of lesions. One of these children does indeed have a history of infantile hypercalcemia. The findings on this patient and the observations made on a patient with infantile hypercalcemia without any cardiac lesion will be published elsewhere.

## Acknowledgment

Our sincerest thanks go to Dr. J. Kenez and his associates for the surgical management of these patients and to Dr. H. Schlange for the psychologic testing of the patients.

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Dec 4, 1964



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News of her safety was received this week from Dr. Helen Donovan, whose work as a missionary doctor in the Congo was described in "Medical Mirror" (August 14, "Faith and hope in the land of the Pygmies"). She has been evacuated from Nebobongo to Ibambi, but the whole area is still in danger from Congolese rebel forces. No news has been heard of another British doctor, Ian Sharpe, since the end of July.

# Vitamin D excess a pregnancy hazard

FROM OUR OWN CORRESPONDENT

MENTAL retardation and certain other abnormalities in babies may be the result of overdoses of vitamin D during the mothers' pregnancy.

This conclusion was reached by a study at Johns Hopkins Hospital, Baltimore. The results showed "very clearly that there is a great potential hazard for some women during pregnancy of excessive intake of vitamin D," said Dr. Robert E. Cooke, the hospital's chief paediatrician.

Dr. Cooke recalled the emphasis placed upon vitamin D in the diet some 30 years ago to prevent rickets. Since then women have been urged by obstetricians to drink large quantities of milk and to eat vitamin-D-rich foods.

The actual recommended intake of the vitamin is only 400 units a day, or the approximate amount contained in one quart of milk.

One woman cited as an example by Dr Cooke ingested 2,000 to 3,000 units of vitamin D a day, drinking nearly two quarts of milk and eating other foods with a high D content. Her child had heart defects, high blood pressure and kidney impairment, as well as being mentally retarded.

In the last 18 months the researchers found 13 children with abnormalities which they attributed to the calcium factor. Physical characteristics of such cases, Dr. Cooke said, included a turned-down mouth, wide space between the eyes, low-set ears, heavily mineralized bones and constricted blood vessels.

Emphasizing that too much vitamin D "is not something that affects every pregnant woman because there is a wide variance of sensitivity" to it, he urged pregnant women to review their diets with their doctors.

Reasonable amounts of the vitamin were acceptable, he continued, but excessive amounts might be unwise. The degree of sunshine a woman received must also be taken into account.

Dr Cooke established that the permeability of body systems was increased by excessive vitamin D. Thus calcium was allowed to be deposited in abnormal quantities in such places as the skull, bone structure and arteries leading to and from the heart.

Since a number of very young infants were found to be so affected, Dr. Cooke and his associates have concluded that the excess amount must have come during the prenatal period.

# 'Choose your own test' brings big response

A SCREENING clinic set up in the town hall, Rotherham, Yorkshire, for one week met with a surprising response from the local population.

The investigations carried out were mass radiography, the copper sulphate test for anaemia, audiometry, cervical smears for cytology and a "do-it-yourself kit" for diabetes mellitus which was taken away for self-testing at home.

Dr. R. J. Donaldson, the MOH, told *Medical News* that the population of Rotherham was 85,000, which could be doubled if the surrounding area was taken into account. In the first four days 2,379 people had attended. They were given a master card on which was written their name and address and that of their general practitioner. They could then choose which tests they wanted.

Of the 2,379 people, 1,808 had a chest X-ray, 1,714 were tested for anaemia (this was carried out by the blood transfusion service), 756 were tested by audiometry, and 778 women had cervical smears taken — Dr. Donaldson said that he had expected to have to cater for only 300.

More than 3,300 diabetes test kits had been handed out, but this high figure was due to people taking them away for relatives.

Dr. Donaldson said that the scheme, which had been in the planning stage for some months, had the approval of the local medical committee. The work was done mainly by his own staff with help from GPs.

Analysis of the results would take time, but Dr. Donaldson was able to say that more women than men had attended; 120 instances of a haemoglobin below 80 per cent., and seven cases of active tuberculosis had been discovered. A lot of pathology in those taking the audiometry test had been uncovered, but careful selection would take place and not everyone would be referred to their GP.

In the case of cervical cytology, the GP would be notified whatever the result. Dr. Donaldson said that a large number of cervical erosions were detected and as a result a consultant had had a whole clinic taken up with their treatment.

## The vulnerable Scotsman

ACCORDING to an article in the *Scottish Medical Journal*, a Scot is 20 times more likely to die of a duodenal ulcer than a Parisian.

Two members of the gastro-intestinal unit at the Western General Infirmary, Edinburgh, say that this is one of the "remarkable differences in the national and geographical prevalence of the disease."

## Diphtheria outbreak

LOS Angeles county health officer Dr. Kenneth Sutherland has expressed concern over what he termed "an abrupt flare-up" of diphtheria.

There had been sixteen confirmed or possible cases in the week since a four-year-old girl died of the disease.

Thirteen of the patients were in two related families, but other cases had appeared "simultaneously but independently." The 13 related patients were all aged under 20.

Dr. Sutherland reported that in none of the cases was the victim previously immunized, and blamed the outbreak on laxity over immunizations because of an erroneous belief that diphtheria was a "rare" disease.

# The pragmatic approach — and its origins

ENGLISH medicine and English philosophy have a common pragmatic approach to the problems which occupy them, writes a *Special Correspondent*.

In this year's Sydenham Lecture, given by Dr. R. R. Trail to the Faculty of the History of Medicine and Pharmacy at Apothecaries' Hall, the origins of this national attitude were traced back to two contemporaries and friends of the late 17th century, Thomas Sydenham and John Locke.

Dr. Trail pointed out that the pleas which have been frequently heard during the 20th century for a return to the patient in his wholeness and uniqueness were really a restatement of the thesis which chemical cures propounded successfully for the first time by Walter Harris in 1689.

Sydenham mistrusted the traditional methods of treatment. In fact he often counselled against any treatment at all. He certainly had a loathing for excessive bleeding, purgations and poisonous concoctions, and much preferred the *vis medicatrix naturae* of Hippocrates.

If specifics were to be employed they must have the sanction of experience carefully gathered—quinine for fever,

Sprain

Prescribe better support, great
less skin maceration. Prescrib

Elastikon porous, adhesive bandage provides:

1 Better suppo... Positive adhesion plus greater elasticity enable Elastikon to give better support to sprained knees, ankles, wrists, etc.

2 Greater comfort The soft, non-adhesive edges ensure that Elastikon will not chafe, stick to clothing, fray or curl at the edges.

3 Less bandag... after pr... ation of

FREE ... tin of E... you w... (Gt. Bri...

Johnson & John...

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# The New England Journal of Medicine

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Established in 1812 as The NEW ENGLAND JOURNAL OF MEDICINE AND SURGERY

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# IDIOPATHIC HYPERCALCEMIA AND SUPRAVALVULAR AORTIC STENOSIS*

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## Documentation of a New Syndrome

RICHARD E. GARCIA, M.D.,† WILLIAM F. FRIEDMAN, M.D.,‡ MICHAEL M. KARACK, M.D.,§ AND RICHARD D. ROWE, M.B.¶

BALTIMORE, MARYLAND

A PECULIAR facies suggesting kinship has been found in some nonfamilial cases of supravalvular aortic stenosis in childhood.[1-6] In addition, it has been recognized that infants with idiopathic hypercalcemia have a rather characteristic "elfin" facial appearance. Recently described are a group of older children with "aortic stenosis" and an "elfin" facies. An illness during infancy in each patient was suggestive of idiopathic hypercalcemia.[2] Their facies appeared identical to those of patients with supravalvular aortic stenosis described by others.[3,5,6] It seems unlikely that this remarkable similarity is coincidental.

Although an association between idiopathic hypercalcemia and supravalvular aortic stenosis has been alluded to in the recent literature[2,6] no proved case has thus far been reported. The purpose of this paper is to present such a case and to establish this association as a clinically recognizable syndrome.

### CASE REPORT

C.S. (J.H.H. 108-01-12), a 9-month-old boy, was admitted for the 2d time to the Harriet Lane Home for evaluation of psychomotor retardation and marked muscular hypotonia.

The family history was pertinent in that an 8-year-old male sibling had severe mental retardation. This sibling suffered primary and secondary apnea at birth, and a convulsive disorder subsequently developed. His facial appearance did not suggest hypercalcemia. He was normotensive and had no cardiac murmur. There was no renal dysfunction; calcium and phosphorus and cholesterol determinations yielded normal results. Roentgenograms of the bones gave no evidence of earlier increased mineralization.

The past history disclosed that the patient was the product of an uncomplicated 9-month gestation. Labor and delivery were normal. The birth weight was 3685 gm. (8 pounds, 2 ounces). The neonatal course was not unusual. He was fed a standard evaporated-milk formula (400 units of vitamin D per quart) and received 1000 units of vitamin D daily as a vitamin supplement. At the age of 5 months he was referred by Dr. A. C. Kolls to the Harriet Lane Home Cardiac Clinic for evaluation of cardiomegaly and cardiac murmur. A diagnosis of valvular pulmonary stenosis was entertained. At 6 months of age an uncomplicated bilateral inguinal herniorrhaphy was performed. At follow-up visits it became increasingly evident that the patient was failing to attain normal developmental milestones. At the age of 9 months he was unable to sit with support or to crawl, and he had a weak cry.

Physical examination showed him to be in the 10th percentile for height and in less than the 3d percentile for weight. The blood pressure was 150/62 mm. of mercury in the right, and 126/60 mm. in the left arm and 110/70 mm. in the lower extremities. The facies was elfin (Fig. 1). Slit-lamp examination disclosed bilateral lenticular opacities compatible with calcium deposition. Marked muscular hypotonia was evident. There was diminished muscle mass, poor motor control and symmetrically hyperactive deep tendon reflexes. Cardiac examination revealed a right precordial lift and a diffuse apical impulse. A systolic thrill was palpable over the upper sternal borders and in the suprasternal notch. The 2d heart sound split normally with respiration, and both aortic and pulmonary-valve closure sounds were easily distinguished. A Grade 4 (on the basis of 6) systolic ejection murmur was heard maximally over the right and left upper sternal borders and radiated over the entire precordium, into the neck and to the back. No manifestations of congestive cardiac failure were present.

The hemogram revealed a mild normochromic, normocytic anemia. Urinalyses showed acid pH, occasional pyuria and microscopical hematuria without bacilluria. Urine cultures were sterile. A 12-hour urine concentration test yielded a specific gravity of 1.015. Standard urea clearance, corrected for body-surface area, was 27 per cent of the normal value for the patient's age. The creatinine clearance was similarly reduced. The serum chemical findings were as follows: sodium, 140 milliequiv., chloride, 100 milliequiv., potassium 4.5 milliequiv., and carbon dioxide combining power, 21 milliequiv. per liter; urea nitrogen, 18 and 30 mg., total lipids, 1.9 gm., total cholesterol, 165 mg., calcium (method of Harrison and Harrison[8]), 13.1 and 13.3 mg., phosphorus, 3.8 and 3.2 mg., alkaline phosphatase, 2.8 Bodansky units, total protein, 6.1 gm., albumin, 3.5 gm., globulin, 2.6 gm., protein-bound hexosamine (method of Winzler[9]), 215 mg., and vitamin D assay (method of Bell et al.[10]), 1540 units per 100 ml. (normal, 60-400 units).

Roentgenologic examination revealed considerable sclerosis of the bony calvaria and base of the skull, as well as diffuse osteosclerosis of the long bones and vertebras (Fig. 2). An intravenous pyelogram was normal. X-ray study of the chest disclosed an increase in the cardiomegaly first noted at the age of 5 months.

An electrocardiogram showed a vertical electric position, right-axis deviation and combined ventricular hypertrophy.

Cardiac catheterization with selective cineangiocardiography was performed. The arterial catheter was advanced to the ascending aorta, but it could not be passed across the aortic valve. The venous catheter was advanced to the main pulmonary artery. The catheterization data are presented in Table 1. There was a systolic gradient of 21 mm. of mercury across the pulmonary valve. A cineangiogram in the left anterior oblique position after injection of contrast material into the main pulmonary artery suggested mild stenosis at the origin of the left pulmonary artery. A thickened, abnormal pulmonary valve was identified. A 2d cineangiogram with the catheter in the ascending aorta distal to the aortic valve (Fig. 3) demonstrated a supravalvular aortic narrowing, with a supravalvular aortic diaphragm, a dilated left coronary artery and mild aortic insufficiency. The wall of the left ventricle appeared strikingly thickened.

Surgical correction of the cardiovascular anomalies was not deemed feasible at this age. The patient was placed on a low-calcium diet with no added vitamin D and was

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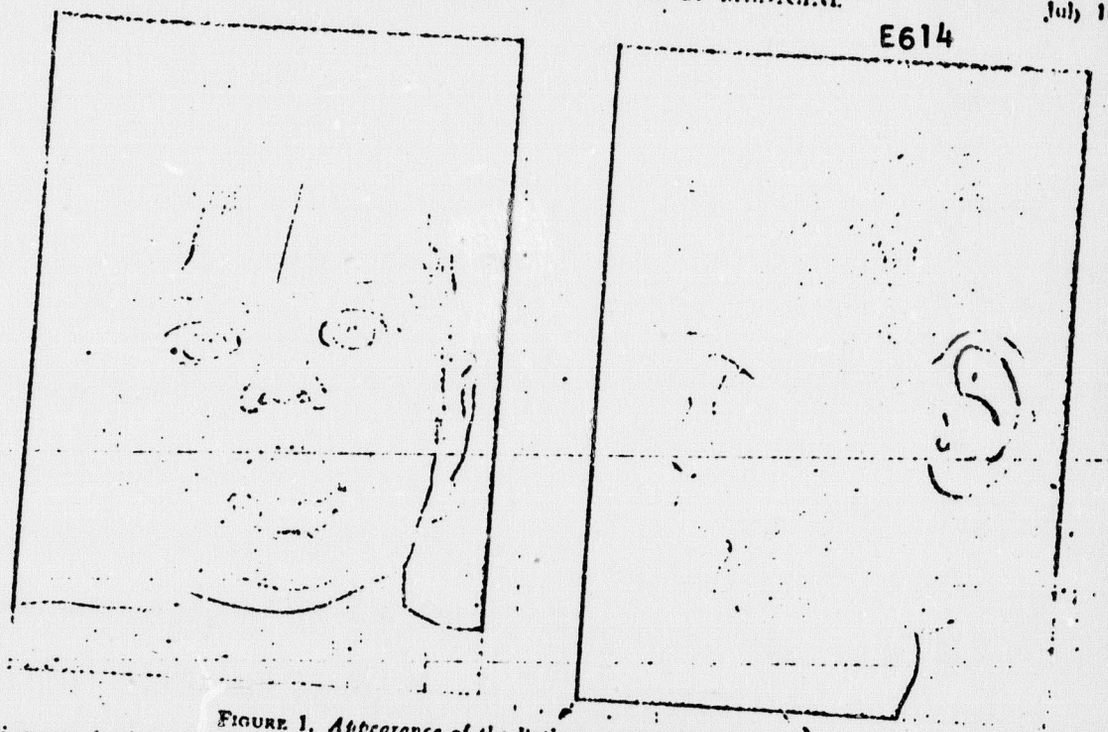


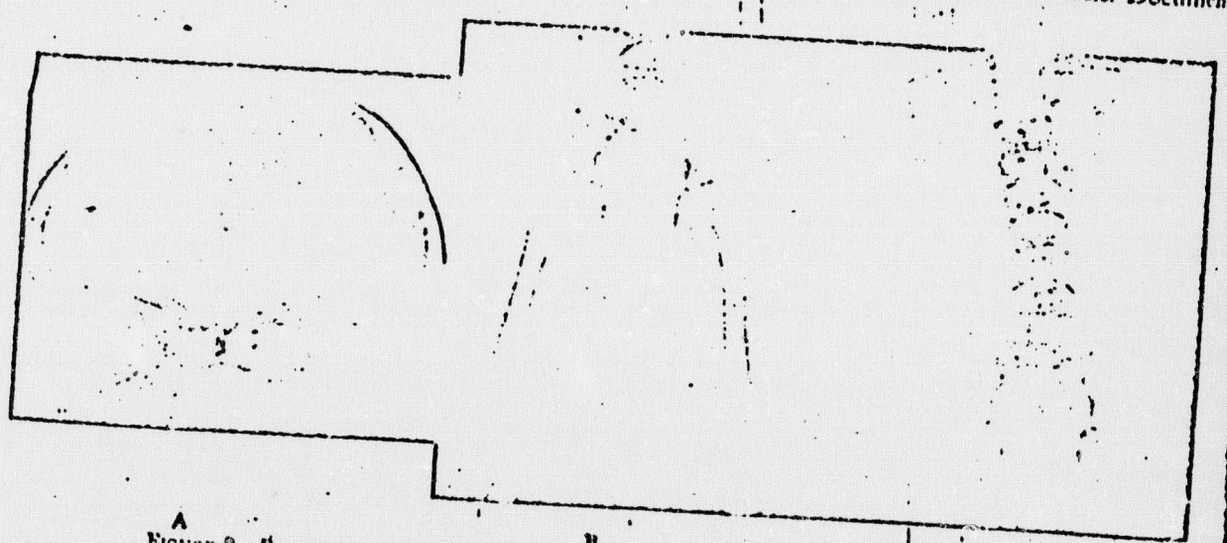
FIGURE 1. *Appearance of the Patient at Nine Months of Age.*
*The physiognomy is characteristically "elfin." Note the high, prominent forehead, epicanthal folds, underdeveloped bridge of the nose and mandible and overhanging upper lip.*

discharged to be followed in the Outpatient Department. The serum calcium determination 3 weeks after discharge was 11.4 mg. per 100 ml.

## DISCUSSION

The syndrome of idiopathic hypercalcemia described by Fanconi et al.[11] consists of growth and mental retardation, irritability, anorexia, vomiting, muscular hypotonia, an elfin facies and generalized osteosclerosis. There is renal dysfunction, often associated with infection, and hypercalcemia, with normal serum phosphorus and normal or low serum alkaline phosphatase levels. Systemic hypertension and cardiac murmurs are common. This syndrome, as well as the milder form described by Lightwood,[12,13] is etiologically related to vitamin D administration and metabolism.[14-17]

Autopsies have not revealed that a congenital cardiac anomaly is the cause of the commonly heard cardiac murmur.[18] Black and Bonham Carter[2] reported a group of cases with the facies of hypercalcemia and the murmur of aortic stenosis. Documen-



A B C

FIGURE 2. *Roentgenograms of the Skull (A), Pelvis and Long Bones (B) and Spine (C).*
*There is appreciable sclerosis of the calvaria and base of the skull, as well as diffuse osteosclerosis, with bands of increased density at the metaphyseal ends of the long bones and the epiphyseal margins of the vertebrae.*

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TABLE 1. *Cardiac-Catheterization Data.*

| Catheter Position | Blood Oxygen Saturation | Pressure |
|---|---|---|
| | % | mm. Hg. |
| Aortic arch | 95 | 110/77 |
| Arch just distal to aortic valve | — | 151/77 |
| Main pulmonary artery | 64 | 29/15* |
| Right ventricle | 57 | 50/2-7 |
| Right atrium | 63, 68, 68 | (A wave, 4) (V wave, 1) (Mean, 2) |
| Superior vena cava | 67 | — |
| Inferior vena cava | 67 | — |

*Main pulmonary-artery pressure tracing normal & thus compatible with unilateral stenosis of main branch of pulmonary artery.[19]

tation of hypercalcemia was absent in all their patients, and the cardiac lesion, supravalvular aortic stenosis, was described in only 1 patient. These authors postulated that the myxomatous thickening of the aorta found in their case and the similar pathological changes found in the aortic valve in the case reported by Rashkind et al.[18] were responsible for the cardiac murmur. The similarity between the cardiovascular abnormality seen in acquired vitamin D intoxication and idiopathic hypercalcemia has also been recognized. Excessive vitamin D administered to animals has been shown to produce changes in the wall of the aorta, coronary arteries and heart valves that range in severity from subendothelial edema to calcification.[20-22] It is interesting that the lesions on the rat and rabbit aorta seem to begin and predominate just above the aortic sinuses.

The triad of mental subnormality, unusual facial features and supravalvular aortic stenosis is now an established clinical syndrome.[1,3,5] It is probable that most, if not all, of the patients thus far described were born with supravalvular aortic stenosis.[5]

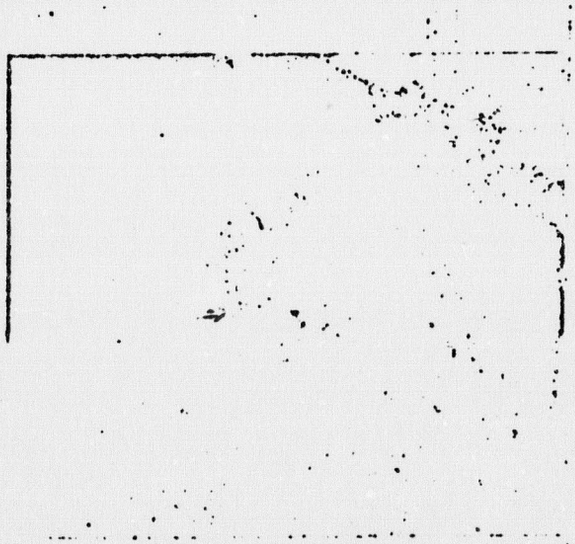

FIGURE 3. *Cineaortogram Taken at Nine Months of Age, Showing Supravalvular Aortic Stenosis (Arrow) a Short Distance above the Aortic Valve.*

*Note the enlarged left coronary artery.*

The findings in the patient described above suggest that idiopathic hypercalcemia is also a feature of this syndrome. It is not yet certain, however, whether the hypercalcemia is one component of a genetically determined multiple-system abnormality or whether the total syndrome stems from a derangement of vitamin D metabolism. The probability that the cardiac lesions in the present case are congenital does not preclude a metabolic disorder *in utero*. The implication is sufficient to warrant a major effort to obtain detailed studies of other patients and their families.

## Summary and Conclusions

An infant with severe idiopathic hypercalcemia associated with supravalvular aortic stenosis and valvular and postvalvular pulmonary stenosis is described. To our knowledge, this represents the first proved association between the aortic lesion and idiopathic hypercalcemia. This case suggests the possibility that idiopathic hypercalcemia is part of the newly recognized syndrome of mental subnormality, a peculiar facies and supravalvular aortic stenosis. The characteristic facies seen in each of the two syndromes appears identical.

Attention is called to the similarity between the cardiovascular lesion seen in experimental vitamin D intoxication and idiopathic hypercalcemia.

Since this paper was submitted for publication complex dental malformations and peripheral pulmonary stenosis have been described in association with the syndrome of supravalvular aortic stenosis, mental retardation and peculiar facies.[23]

We are indebted to Dr. Harold E. Harrison for performing the serum calcium determinations, to Dr. Olga Baghdassarian for reviewing the roentgenograms and to Dr. Robert E. Cooke for his helpful suggestions. Mr. Walter Hooper and Mr. Glen Shue, of the United States Food and Drug Administration, Washington, D. C., kindly performed the vitamin D assay.

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# CATECHOL AMINE METABOLISM IN ESSENTIAL HYPERTENSION*

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BECAUSE both norepinephrine and sympathetic stimulation produce vasoconstriction, there has been much speculation about the role of norepinephrine in essential hypertension. Hypertensive patients have been shown to be more sensitive to infused norepinephrine than normal persons.[1] More recently drugs that affect either the tissue levels or the metabolism of norepinephrine or other catechol amines have been shown to have marked antihypertensive effects.[2]

The majority of reported studies of catechol amine *excretion* in hypertensive patients indicate normal or moderately elevated values for urinary catechol amines.[3-11] Several studies have shown significantly *lower* excretion in hypertensive patients than in normal persons.[12-16] Vanillylmandelic acid (VMA) excretion in hypertensive patients has been reported as normal,[2,10,17] elevated[18] or low.[16] Determination of the O-methylated derivatives of epinephrine and norepinephrine, metanephrine and normetanephrine respectively has shown no difference between hypertensive patients and normal controls.[2,10,17,19]

It seems that the most valid approach to the study of catechol amine metabolism in essential hypertension would be to investigate the urinary excretion of catechol amines and catechol amine metabolites by the most specific and sensitive procedures available. Ratios between the various metabolites should be determined as well as absolute rates of excretion. Such ratios[20] are useful in that the marked variation in the absolute amount of catechol amines excreted may mask significant changes that could be identified if the relative amounts of the various metabolites were compared.

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## METHODS

The urinary excretion of catechol amines and their metabolites was studied in 73 patients with essential hypertension and in 47 apparently normal persons with normal blood pressures. None of the hypertensive patients had taken medications for at least four weeks before the urine was collected.

Thirty-eight of the hypertensive patients were out-patients of the Hypertension Clinic, and 35 were in-patients on the medical wards. They were not selected except for the exclusion of those on medications. The normal control group consisted of laboratory and hospital personnel and their relatives. None of the normal subjects were taking medications. All subjects were ambulatory during the collection period but did not engage in any strenuous activity such as climbing stairs. Although diet was not controlled, none of the subjects had recently eaten bananas. The majority of the specimens were collected in the late morning or just before lunch. The laboratory methods used were as follows:

### Epinephrine (E) and Norepinephrine (N)

The free (unconjugated) catechol amines were determined, amberlite CG-50 (ammonium ion form) being used for the initial separation. The catechol amines were oxidized with potassium ferricyanide at pH 5.5 and tautomerized to form indoles by the addition of an alkaline ascorbate solution stabilized with ethylenediamine. Internal standards of both epinephrine and norepinephrine were used for each determination. All the oxidations were done in duplicate. Fluorescence measurements were made with a modified Farrand filter fluorometer with the use of two sets of interference filters, one with an excitation wavelength of 390 millimicrons and a fluorescence wavelength of 500 millimicrons and a second set with wavelengths of 430 and 520 millimicrons respectively.[21]

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# Supravalvular Aortic Stenosis

## *Underdevelopment and Characteristic Facies*

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Congenital supravalvular aortic stenosis is due to a variety of anomalies in the proximal portion of the ascending aorta. Clinically, however, the most important lesion is a circular constriction of the aortic wall above the valve cusps. In certain patients with this type of anomaly, the supravalvular aortic stenosis constitutes one element of a clinical syndrome marked also by impaired growth, mental deficiency, and a characteristic facial appearance. Three patients with the features of this syndrome have been seen in this hospital since 1955. The purpose of this report is to present these patients whose syndrome was first described by Williams et al in New Zealand.

## Case Reports

CASE 1.—Patient 1 was seen at 8 years of age. He was born prematurely and his physical growth and mental development were retarded. He had frequent respiratory infections, exertional dyspnea, and fatigue for several years. A heart murmur was discovered at the age of 2½ years. Two of his six siblings were also mentally retarded.

Physical examination revealed the development to be below the third percentile: height, 44 inches (111.8 cm); weight, 37 lb (16.8 kg); head circumference, 18¼ inches; chest circumference, 22 inches. Mild webbing of the scapulae, dorsum rotundum, mild cubitus varus, and interdigital webbing of the fingers were also present. The cardiac apical impulse was forceful. It was palpable over the upper sternum and carotid arteries. A grade 4/6 systolic ejection murmur was heard loudest in the right second intercostal space. It was transmitted throughout the chest and to the carotid arteries. The amplitude of the right arm pulses was more than the left. The blood pressure was 120/80 mm Hg in the right arm and 98/70 mm Hg in the left arm. His unusual facial features were not recognized. However, study of the photographs (Fig 1) shows the divergent strabismus and the coarse pouting lips which are not family features. A psychometric examination indicated a mental age of 4 years and an IQ of 47.

The ECG showed left ventricular hypertrophy. The radiographs demonstrated a bone age of 3 years. A retrograde left ventricular angiogram, done when he was 13 years, outlined an annular constriction of the ascending aorta immediately above the origin of the coronary arteries (Fig 2). The left ventricle was hypertrophied. The coronary arteries were normal.

Open heart surgery was performed at the age of 14 years and the angiocardiographic findings were confirmed. A Teflon patch was sutured in a vertical incision made through the constricted area. At the time of operation, the peak systolic pressure gradient between the left ventricle and the aorta distal to the constriction was 145 mm Hg before and 100 after the procedure. The postoperative course was complicated by pneumonia and *Staphylococcus aureus* septicemia with abscess formation at the site of the prosthesis. A false aneurysm formed at the root of the aorta and later began to leak. An attempt to resect the aneurysm was unsuccessful and the patient died.

The postmortem examination revealed fibrinous thickening of the epicardium and pericardium and inflammatory changes in the region of the base of the heart. There was left ventricular hypertrophy with a myocardial thickness of 22 mm and a small ventricular cavity. The left coronary and noncoronary cusps were normal. The right coronary cusp was hypoplastic and fused at its superior margin to the aortic wall, making a pouch from which the coronary artery originated. This pouch communicated with the aortic lumen only through

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Fig 1.—*A*, case 1. *B*, snapshot of the patient among his siblings emphasizes that his abnormal appearance is not a family characteristic.

a 1 mm ostium. The aortic valvular circumference was 4.5 cm. The circumference of the aorta at the level of the patch was 2.2 cm and distal to it, 2.8 cm.

CASE 2.—The patient was 8 years old. She had a heart murmur heard at the age of 6 months but remained active and asymptomatic. Her growth and mental development were slow.

Physical examination revealed physical development to be below the third percentile: height, 43½ inches (111.8 cm); weight, 38 lb (17.2 kg). Her facial appearance was entirely different from that of her only sibling (Fig 3). The characteristic features of her face were a broad forehead, esotropia of the left eye, depressed bridge of the nose, full cheeks, and coarse pouting lips. The

Fig 2 (case 1).—Left ventricular and supravalvular angiograms demonstrate the lesion.

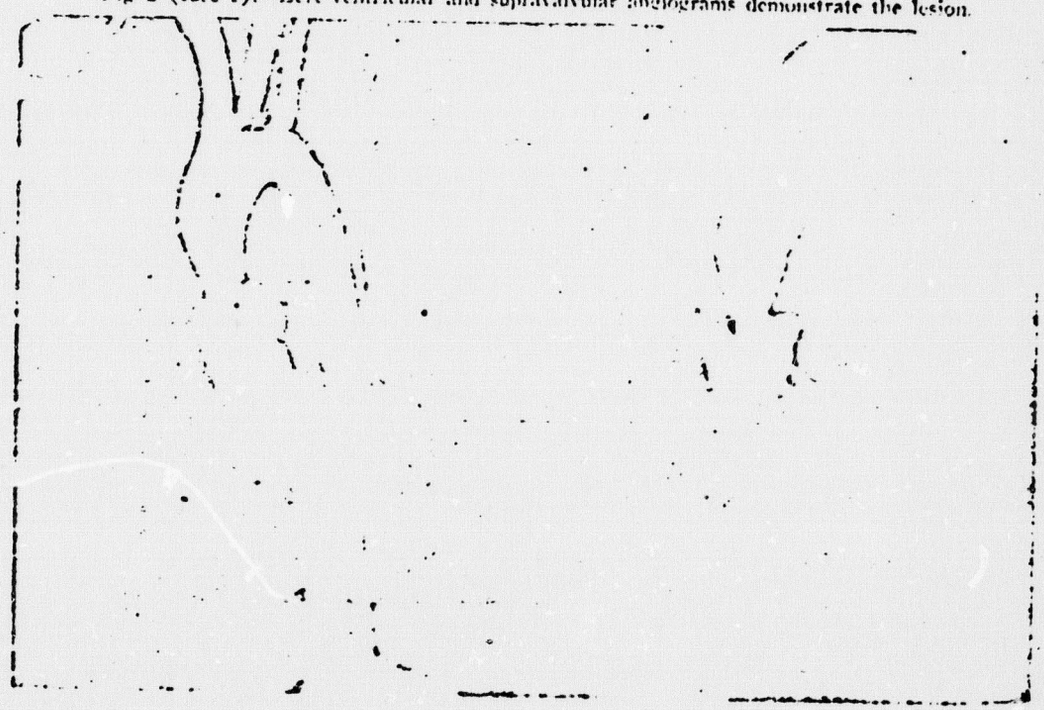

Fig 3.—Case 2 has facies characteristic of this syndrome. Her sister is seen with a normal face.

heart size was normal. A systolic thrill was palpable over the right first and second intercostal spaces, suprasternal notch, and carotid arteries. A grade 5/6 systolic ejection murmur was audible best in the right second intercostal space and was well transmitted to the neck. There was a right inguinal hernia. In her fine movements, slight incoordination was noted. A psychometric examination revealed a mental age of 4½ years and an IQ of 60.

The chest radiograph showed a concavity at the right upper border of the cardiac shadow. The left ventricular angiograms demonstrated hypertrophy and dilatation of the left ventricle. There was a circular narrowing in the ascending aorta immediately above the origin of the coronary arteries with a slight poststenotic dilatation (Fig 4).

Open heart surgery was performed during which the coarctation and other angiocardiographic findings were confirmed. The aortic wall was thickened. The aortic cusps were normal. A patch of woven Teflon was inserted in the stenotic area. The peak systolic pressure gradient between the left ventricle and the femoral artery, at the time of operation, decreased from 75 mm Hg prior to the procedure to 35 following it.

A postoperative left ventricular catheterization revealed a 40 mm Hg peak systolic pressure gradient in the ascending aorta across the stenosis (Fig 5). She remains asymptomatic.

Case 3.—Patient 3 was seen at the age of 8 years. He was born prematurely as the fourth

Fig 4 (case 2).—Left ventricular angiograms outline the hourglass appearance of the supravalvular aortic constriction.

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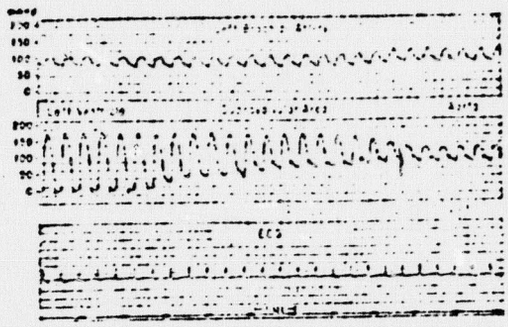


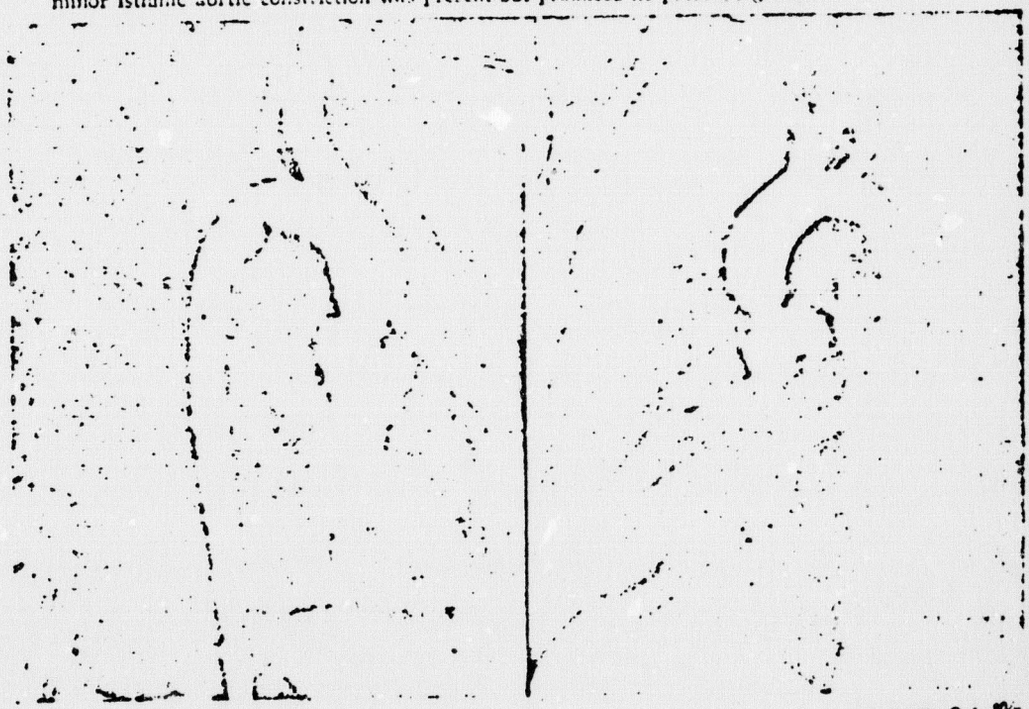
Fig 5 (case 2).—The withdrawal pressure tracing from the left ventricle to the aorta above the stenosis.

Fig 6 (case 3).—Photograph of patient and two half-brothers emphasizes the characteristic specificities of the face in this syndrome.

child of the mother and the only child of this family. A heart murmur was heard at 6 weeks of age. His growth and mental development were slow. He was active and asymptomatic.

Physical examination revealed a highly verbal but mentally retarded child with physical development between the 10th and 25th percentile. He was 49½ inches (124.5 cm) tall and weighed 51 lb (23.1 kg). He had characteristic facial features consisting of esotropia of the right eye, coarse full cheeks, depressed broad nasal bridge, and thick pouting lips (Fig 6). The supravalvular location of the aortic stenosis was clinically suspected from his facial appearance. He had mixed astigmatism of both eyes. A marked carious destruction of his permanent teeth was noted. A systolic thrill was felt in the right first and second intercostal spaces, in the suprasternal notch, and over the carotid arteries. The apical impulse was forceful and palpable in the fifth intercostal space 9 cm from mid-

Fig 7 (case 3).—Left ventricular and aortic angiograms demonstrating supravalvular stenosis. Regurgitation of the contrast substance into the left atrium indicates mitral insufficiency. A minor isthmic aortic constriction was present but produced no pressure gradient.



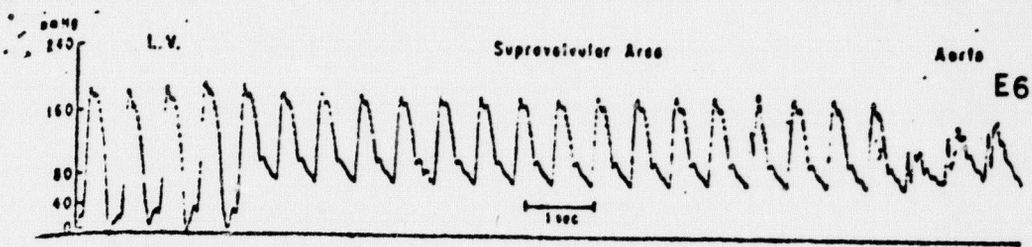



Fig 8 (case 3).—The withdrawal pressure tracing across the aortic valve and supravalvular area.

line. There was a grade 4/6 systolic ejection murmur audible in the right second intercostal space which radiated to the neck and spine. The aortic closure sound was increased. The blood pressure was 125/60 mm Hg in the right arm and 110/50 mm Hg in the left arm. There was a mild hypertonicity of the legs. A psychometric examination revealed a mental age of 4½ years and an IQ of 53.

Left ventricular angiography demonstrated a circular obstruction immediately above the origin of the coronary arteries (Fig 7). In addition, it also showed slight mitral regurgitation. The aortic valve was normal. The left carotid arose from the innominate artery. There was a 40 mm Hg peak systolic pressure gradient across the stenotic area (Fig 8). He remains asymptomatic.

## Comment

The findings in our three patients and in eight others reported by Williams [2] and Beuren [3] indicate the presence of a rare congenital syndrome which consists of supravalvular coaretation of the aorta, mental retardation, physical underdevelopment, and a characteristic facial appearance.

The cases already recognized have all been children between the ages of 5 and 12 years. However, the diagnosis can be made during infancy, since the cardiac murmur is present at birth and the other features become evident during the first year of life.

Prematurity and low birth weight have been common but not constant features of this syndrome. Two of our patients were premature.

Inadequate physical and mental development are constant elements and present since birth. Failure to thrive becomes obvious to the family in early childhood and constitutes their only complaint in the absence of cardiac symptoms. The degree of mental deficiency in the reported patients has varied from mild to moderate with intelligence quotients ranging from 42 to 72. It is of interest that prior to the recognition of this syndrome, mental retardation was noted to be frequently associated with supravalvular aortic coarctation. Moreover, in all reported patients with annular supravalvular aortic stenosis not associated with skeletal features of Marfan's syndrome, mental retardation has accompanied physical underdevelopment. It should be added that the absence of mental retardation in isolated supravalvular aortic coarctation as well as its relative infrequency with other types of aortic stenosis suggests that the mental insufficiency is not a simple consequence of the aortic obstruction.

An interesting element of this syndrome is the striking facial appearance. This is sufficiently characteristic as to permit a bedside prediction of the aortic lesion as has been our experience in the third patient and those of Williams and Beuren and their associates. The prominent features of the abnormal facies consist of esotropia, broad and depressed nasal bridge, coarse pouting lips, and heavy cheeks. The resemblance of these patients to one another and their dissimilarity to their own family members is evident.

The supravalvular aortic stenosis represents the most important part of this syndrome causing symptoms and limiting the longevity of these patients. Among the various anatomic types of this anomaly, the annular constriction of the aortic wall at the origin of the coronary arteries has been the only variety seen in all of the reported cases.

Mencarelli [4] first described this anomaly, and its pathology was fully studied by Perou [5] who classified it as "true" supravalvular aortic stenosis. Other obstructive lesions of the aortic root such as membranes or fibrous bands, if not combined with coaretation, bear no known relationship to this syndrome. The degree of obstruction varies from mild to moderately severe. The peak systolic gradient, obtained at the time of surgery or during left ventricular catheterization in the 11 published cases has ranged from 38 to 160 mm Hg. The cardiac symptoms have shown no proportional relation to the systolic gradient across the stenotic area. None of the patients reported by Williams had any cardiac symptoms and their gradients changed from 38 to 100 mm Hg. Bearen's cases, however, were all limited in exertion and had gradients ranging between 50 and 160 mm Hg. Our first patient with gradient of 145 mm Hg had limited exercise tolerance. The other two with gradients of 75 and 40 mm Hg were free from any symptoms.

It is of note that supravalvular aortic coaretation has been repeatedly found as an isolated lesion without the presence of other elements of this syndrome. We have observed two patients, age 6 and 13 years, with gradients of 130 and 110 mm Hg across the supravalvular coaretation. They were both normal in development, intelligence, and facial appearance.

In addition to these major features, our patients have all shown variable degrees of carious destruction of their teeth. Our second patient had slight incoordination in her movements. The third one exhibited hypertonicity of the lower extremities.

This syndrome is congenital in origin but its etiology remains unknown. Hypercalcemia of infancy [6] has been suggested as a possible cause. Chromosomal studies [7] have revealed no abnormality.

## Summary

A syndrome is described which includes supravalvular coaretation of the aorta, a characteristic facial appearance, impaired growth, and mental deficiency. The patients with this syndrome may become restricted in their activity in childhood and eventually develop cardiac failure.

The diagnosis can be made on physical examination. This reveals a peculiar, but characteristic facies, signs of obstruction of the left ventricular outflow, and physical and mental underdevelopment.

The three patients presented in this article bring the total number of the reported cases to 12.

This syndrome is congenital and the etiology is unknown.

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# The syndrome of idiopathic hypercalcemia of infancy with associated congenital heart disease

*The relationship of idiopathic hypercalcemia of infancy with the syndrome of supravalvular aortic stenosis and/or peripheral pulmonary stenosis, mental retardation, and peculiar facies has been emphasized in the recent literature. There remains, however, a paucity of reported instances in which the hypercalcemia was documented. Two patients are described in whom the diagnosis in infancy was idiopathic hypercalcemia with associated congenital heart disease. Recent revaluation of the cardiac lesions demonstrated isolated supravalvular aortic stenosis in one case and isolated peripheral pulmonary artery stenoses in the other case. There was no maternal history of excessive vitamin intake during pregnancy in either case.*

Kenneth L. Jue, M.D.,* George R. Noren, M.D., and Ray C. Anderson, M.D.**

MINNEAPOLIS, MINN.

RECENT REPORTS in the literature have emphasized a syndrome characterized by peculiar facies, mental retardation, dental malformations, and associated supravalvular aortic stenosis and/or peripheral pulmonary artery stenosis.[1-4] Hooft, Vermassen, and Blancquart[5] and Black and Bonham Carter[6] have considered the facial appearance of these patients to be similar to that seen in patients with infantile idiopathic hypercalcemia. Moreover, on reviewing the early clinical histories of older patients with peculiar facies, mental retardation and aortic murmurs, they encountered many of the clinical features characteristic of patients with idiopathic hypercalcemia in infancy. There was, however, no laboratory documentation of hypercalcemia in their cases. Garcia and associates[7] have subsequently described a 9-month-old infant with documented idiopathic hypercalcemia and both supravalvular aortic stenosis and peripheral pulmonary artery stenosis. Beuren and associates[3] have also reported a patient with supravalvular aortic stenosis, peculiar facies, mental retardation; and a history of infantile hypercalcemia.

This communication concerns 2 patients, aged 9 and 5 years, recently restudied at the University of Minnesota Hospitals, in whom the diagnosis in infancy of idiopathic hypercalcemia and associated congenital

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heart disease had been made. Neither patient has hypercalcemia at the present time.

## CASE REPORTS

Case No. 1. This 9-year-old white female, the product of a full-term pregnancy and uncomplicated delivery, weighed 7 pounds, 7 ounces at birth. There was no history of excessive intake of vitamins by the mother during this pregnancy.

She was referred to the University of Minnesota Hospitals at the age of 6 months because of failure to thrive, poor oral intake, and recurrent vomiting. The significant findings were an elevated blood urea nitrogen and a cardiac murmur. When hospitalized at the age of 8 months, muscular hypotonia was noted. The cardiac murmur was interpreted by one observer as representing subaortic stenosis. Serum calcium, phosphorus, and alkaline phosphatase determinations were within normal limits on two occasions. The blood urea nitrogen was 34 mg. per cent. An intravenous pyelogram demonstrated poor excretion of the opaque material, but no anatomic abnormalities were visualized.

At 14 months of age, she was seen again because of failure to thrive, poor oral intake, frequent vomiting, constipation, psychomotor retardation, and muscular hypotonia. The "elfin-like" facies was particularly noticeable at this time (Fig. 1). Serum calcium and phosphorous were elevated to 14.5 and 6.8 mg. per cent, respectively. The alkaline phosphatase was normal

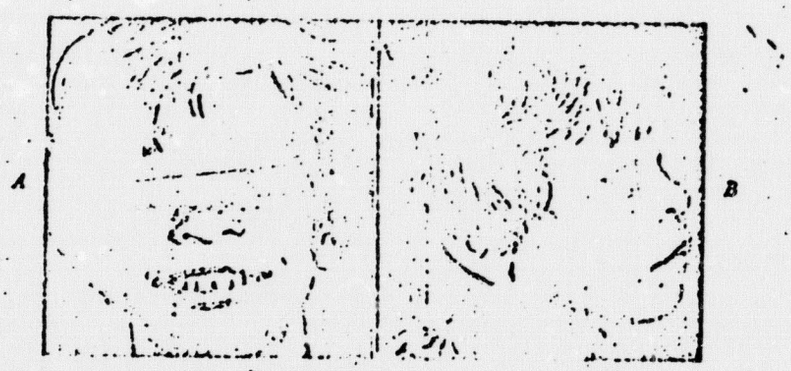


Fig. 1. Case No. 1 at age 9 years. *A*, Frontal view. Note unusual facies with wide mouth. Strabismus has been corrected. *B*, Lateral view. Note flat bridge and stubby nose.

Fig. 2. Case No. 1. *A*, Lateral view of skull at age 14 months. Note marked increase in density of calvarium. *B*, Frontal view of pelvis at age 14 months. Note increased density of bones. These changes in the skull and pelvis had regressed by age 3 to 4 years.

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and the blood urea nitrogen was elevated to 53 mg. per cent. Urinalysis showed an acid pH, no protein, and no cells. Urine culture was sterile. Roentgenograms of the long bones, pelvis, and skull demonstrated increased density and sclerotic changes of the bony structures (Fig. 2). The patient's height, weight, and head circumference were below the third percentile for age. The diagnosis of idiopathic hypercalcemia was made and the patient was admitted for further evaluation. Laboratory findings included: Serum Na 144 mEq. per liter, K 4.4 mEq. per liter, Cl 106 mEq. per liter, $HCO_3^-$ 23 mEq. per liter, ESR 55 mm. per 60 min. (Westergren method), total protein 6.7 Gm. per 100 ml., albumin 3.5 Gm. per 100 ml., globulin 3.2 Gm per 100 ml., BUN 48 mg. per 100 ml, serum cholesterol 166 mg. per 100 ml., and serum carotene 399 µg per 100 ml. The urine Sulkowitch test was positive. Urinary excretion of calcium was 56 to 81 mg. per 24 hours and urinary excretion of phosphorus was 170 to 257 mg. per 24 hours. Vitamin A tolerance test was normal. Creatinine clearance was 14 per cent of normal.

No change in serum calcium was observed over a 3 month period while the patient received a low calcium diet. Cortisone acetate, 10 mg. three times daily, was given over a period of 6 weeks with a slight decrease in serum calcium. The serum calcium returned to normal at 22 months of age while the patient was still receiving small doses of cortisone and remained normal when cortisone was discontinued (Fig. 3). All subsequent determinations of calcium have been normal as have numerous determinations of alkaline phosphatase. Vitamin D was given in doses of 250 and 500 units for 6 weeks without the production of hypercalcemia. An open renal biopsy demonstrated focal renal scarring with minimal calcium deposition. While in the hospital, the patient passed a bladder stone and a second stone was removed at cystoscopy. Chemical analysis of the calculus revealed carbonate and phosphate. Roentgenograms of the chest and electrocardiograms were interpreted as normal at the age of 2 years.

The patient continued to be followed in the cardiac clinic with a diagnosis of either a small ventricular septal defect or aortic valvular stenosis. Psychometric examination at the ages of 4 and 7 years revealed an IQ of 50. Right heart catheterization at the age of 43 months was within normal limits. A left heart study was not performed.

She was admitted to the University of Minnesota Hospitals for further studies in June, 1961. The clinical diagnosis was supravalvular aortic stenosis and possible peripheral pulmonary

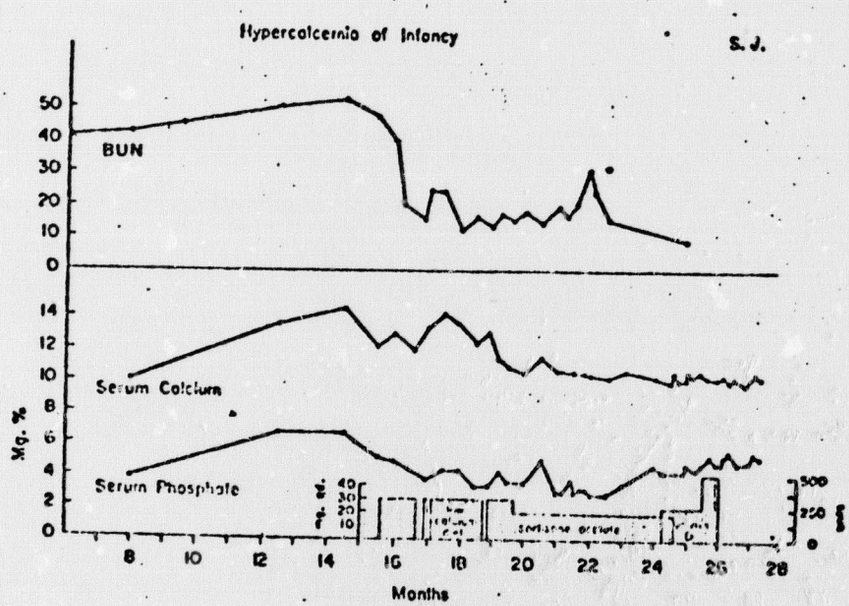


Fig. 3. Case No. 2. Summary of serum calcium, phosphate, and blood urea nitrogen (BUN) values during infancy. (See text for interpretation.)

artery stenosis. Physical examination revealed a thin cheerful child with a peculiar hoarse metallic voice. The "elfin-like" facies remained (Fig. 1). The strabismus had been surgically corrected the previous year. Funduscopic examination was normal. The teeth were markedly carious, but no specific dental malformation was noted. Cardiac examination revealed a thrill in the suprasternal notch and a prominent left ventricular impulse. A Grade 3/4 harsh systolic ejection murmur was heard best along the right upper sternal border. The second sound was normally split; no diastolic murmur or systolic ejection click was noted. A moderate difference in auscultatory blood pressure was noted between the arms, 120/90 in the right arm and 100/70 in the left arm. Electrocardiogram was interpreted as showing left ventricular preponderance and chest roentgenograms were interpreted as normal (Figs. 4 and 5).

Right heart catheterization showed normal findings, with no evidence of pulmonary artery stenosis (Table I). Retrograde left heart catheterization from the right brachial artery showed a marked obstruction just above the aortic valve. The catheter tip was advanced across this obstruction and into the left ventricle on several occasions while a continuous pressure tracing was obtained. A 100 mm. Hg peak systolic pressure difference was present between the supravalvular region and the aorta distal to the obstruction (Fig. 6). A selective left ventriculogram demonstrated an area of marked stenosis immediately above the aortic valve (Fig. 7, *a*). The ascending and descending aorta were hypoplastic. This was especially evident on the lateral film (Fig. 7, *b*). The coronary arteries did not show the dilatation that is frequently seen in this condition, but the aortic sinuses were slightly dilated.

Case No. 2. This 5-year-old white female, the product of a full-term uncomplicated pregnancy, weighed 6 pounds, 6 ounces at birth. There was no history of excessive vitamin intake during this pregnancy. A cardiac murmur was first heard during the newborn examination.

She was referred to the University of Minnesota Hospitals at the age of 3 months because of a cardiac murmur, severe irritability, and recurrent episodes of vomiting. A Grade 2 (on the basis of 1-4) systolic murmur was best heard along the left sternal border but was well transmitted to the back. Roentgenograms of the heart and electrocardiogram were normal. Because of

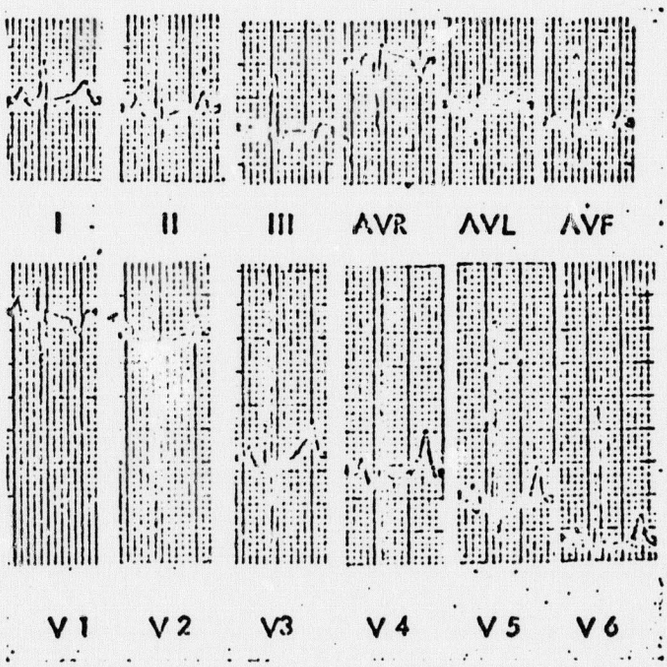


Fig. 4. Case No. 1. Electrocardiogram at age 9 years. Deep S wave in lead $V_6$ suggests left ventricular preponderance, otherwise within normal limits.

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a 30 mm. Hg flush pressure difference between the upper and lower extremities, an aortogram was performed and this showed no significant abnormalities.

At 9 months of age, the patient was seen again because of failure to thrive, irritability, and frequent vomiting. A peculiar "elfin-like" facies,

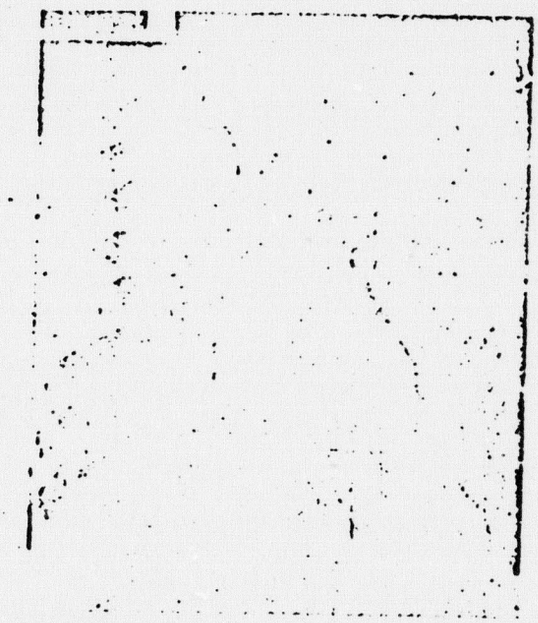

Fig. 5. Case No. 1. Frontal roentgenogram at age 9 years. Note absence of any significant "aortic knob." Cardiac configuration is normal.

hypertelorism, and epicanthal folds suggested a diagnosis of idiopathic hypercalcemia, but serum calcium, phosphorus, and blood urea nitrogen were normal. Four months later the patient was hospitalized because of tachycardia and failure to thrive. The murmur at this time was suggestive of pulmonary stenosis. The serum carotene determination was elevated to 360 μg per 100 ml. Total protein was 7.0 Gm. per 100 ml., with albumin 3.7 Gm. and globulin 2.3 Gm. per 100 ml. Serum calcium, phosphorus, and blood urea nitrogen were once again within normal limits.

At 23 months of age, the patient was hospitalized for surgical correction of a prominent esotropia of the right eye. The facial appearance at this time demonstrated many features of patients with idiopathic hypercalcemia; namely, broad epicanthal folds, flat nasal bridge with upturned nose, and long overhanging upper lip. She was below the third percentile for height and weight. It was apparent that the child was retarded. She did not crawl, walk, or use words. A Grade 3/4 harsh systolic ejection murmur was present in the second and third intercostal space along the left sternal border. This was interpreted as representing pulmonary stenosis. Serum calcium was elevated on several occasions to between 11.0 and 11.7 mg. per 100 ml. Serum phosphorus, alkaline phosphatase, and blood urea nitrogen were normal. She was given a diet containing only 300 mg. of phosphorus and 1 Gm. of calcium. The serum calcium decreased to levels between 8.0 and 8.5 mg. per 100 ml. Serum cholesterol was 167 mg. per 100

Table I. Cardiac catheterization data

| Catheter position | Blood oxygen saturation (%) | | Pressure (mm. Hg) | |
|---|---|---|---|---|
| | Case No. 1 | Case No. 2 | Case No. 1 | Case No. 2 |
| Aortic arch | | | 120/70 | 120/65 $\overline{75}$ |
| Aorta just distal to aortic valve | | | 200/50 | 120/60 |
| Left ventricle | | | 200/0-20 | 120/0-10 |
| Right brachial artery | 100 | 98 | 150/75 $\overline{105}$ | 150/70 $\overline{100}$ |
| Superior vena cava | 75 | 64 | | |
| Mid right atrium (lateral wall) | 78 | 64 | 5/3 $\overline{4}$ | |
| Inferior vena cava | 82 | 70 | | |
| Right ventricle (inflow) | 74 | 63 | 28/10 | 40/0-8 |
| Right ventricle (outflow) | 76 | 65 | | |
| Main pulmonary artery | 77 | 62 | 25/10 $\overline{18}$ | 40/12 |
| Right pulmonary artery (proximal) | | 64 | | 30/15 |
| Right pulmonary artery (distal) | | | 25/10 | 20/10 |
| Right pulmonary artery (wedge) | No flow | No flow | $\overline{10}$ | $\overline{15}$ |
| Left pulmonary artery | | | 25/10 | 28/15 |

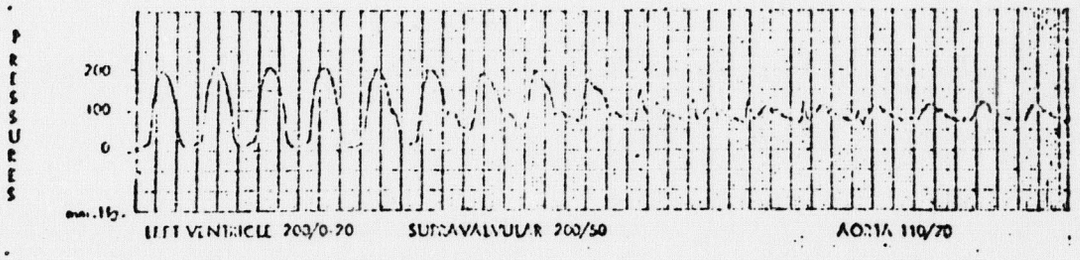


Fig. 6. Case No. 1. Withdrawal pressure tracing from the left ventricle to ascending aorta demonstrating change in diastolic pressure at the aortic valve and change in peak systolic pressure at the site of supravalvular stenosis.

Fig. 7. Case No. 1. *A*, Frontal view of left ventriculogram during diastole. An area of marked stenosis is present immediately above the origin of the coronary arteries. Coronary arteries are of normal caliber. Distal to the area of stenosis, the aorta is hypoplastic. The left subclavian artery is hypoplastic. *B*, Lateral film. The area of stenosis and the hypoplasia of the entire aorta distal to the obstruction is better visualized. Arrow points to dilated aortic sinus. All the aortic sinuses appear dilated. Slight mitral regurgitation into the left atrium due to premature ventricular contractions.

ml. Serum carotene remained elevated. The vitamin A tolerance test was normal. Roentgenograms of the pelvis and long bones did not reveal any areas of increased density or sclerotic changes.

At 31 months of age, the patient was hospitalized again and multiple serum calcium determinations were performed. On several occasions the calcium level was elevated to between 11.0 and 11.5 mg. per 100 ml. Subsequent serum calcium determinations were within normal limits. The serum cholesterol, alkaline phosphatase, and blood urea nitrogen were within normal limits. Psychological testing at the age of 4½ years revealed an IQ of 50.

The patient was hospitalized in August, 1961, for further cardiac studies. Physical examination revealed a small 5-year-old girl with a peculiar facial appearance (Fig. 8). The bridge of the nose was flattened and the tip upturned. Strabismus of the right eye was present. The mouth was held open most of the time. The upper lip was long and overhanging and the palate was highly arched. The teeth were carious but no specific dental malformation was noted. Her voice had a prominent hoarse metallic quality. The height and weight were at the tenth percentile for age. Cardiac examination revealed no palpable thrill or unusual pulsation. A Grade 2/4 systolic ejection murmur was best heard along the upper left sternal border with good radiation to the back and axillae. No ejection

Fig. 8. Case No. 2 at the age 5 years. *A*, Frontal view. Strabismus of the left eye, mouth held open, thickened upper and lower lips. *B*, Lateral view. Note rather flat bridge of nose.

click or diastolic murmur was heard. The second heart sound was normal. A diagnosis of peripheral pulmonary artery stenosis was made.

The roentgenogram of the chest and electrocardiogram were normal (Figs. 9 and 10*A*). The vectorcardiogram suggested right ventricular preponderance (Fig. 10*B*). Right heart catheterization showed no evidence of an intracardiac shunt. A pressure change was noted when the catheter tip was advanced from the main into the right upper pulmonary artery (Table I). Several branches of the left pulmonary artery were entered but no pressure change was noted. A right ventriculogram demonstrated several areas of stenosis of the right upper pulmonary artery with poststenotic dilatation (Fig. 11).

A retrograde left heart study was performed from the right brachial artery; no pressure difference was noted across the aortic valve (Table I). A left ventriculogram demonstrated no evidence of supravalvular aortic stenosis but there was minimal narrowing of the ascending aorta. The excursions of the aortic valve appeared to be limited to a slight extent.

## COMMENT

The syndrome of supravalvular aortic stenosis and/or peripheral pulmonary artery stenosis with peculiar facies and mental retardation appears to be a distinct clinical entity. From the clinical evidence presented by Black and Bonham Carter,[6] Hoedemaeker, Timmermans, and Blanc quart,[5] and the subsequent publication of documented cases of hypercalcemia in patients with this syndrome,[8,9] it appears that idiopathic hypercalcemia is or can be an important associated feature of this syndrome. Since the peculiar facial appearance is an essential feature of this entity, the syndrome under discussion would be expected to occur in those cases of idiopathic hypercalcemia of infancy of the severe type as postulated by Black and Bonham Carter,[6] and not in the vitamin D sensitive, transient form of Lightwood[7] and Payne[8] in which the peculiar facies is not a usual finding.

The possibility that all cases of supravalvular aortic stenosis and/or peripheral pulmonary artery stenosis with mental retardation and peculiar facies represent patients with idiopathic hypercalcemia of infancy remains a most provocative thought. This would then represent a specific metabolic disturbance. Since the cardiac lesion may be present at birth, as suggested in many instances by the presence of a cardiac murmur in the newborn period, the possibility of a metabolic disorder during fetal life must be considered. The exact cause and effect of hypercalcemia alone or in the syndrome under discussion remains unclear at the present time. Induction of hypercalcemia in experimental animals during various stages of pregnancy may yield more information on this point. There could well be a critical time for insult to the fetus, as in the maternal rubella syndrome. This would be con-

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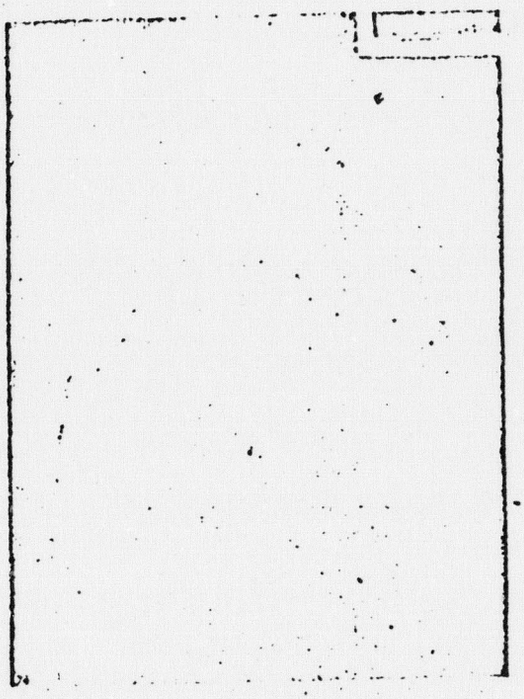

Fig. 9. Case No. 2. Frontal roentgenogram of the chest, normal.

sistent with the observation that only a minority of cases of idiopathic hypercalcemia manifest the cardiac lesions of supravalvular aortic stenosis and/or peripheral pulmonary artery stenosis. Rashkind, Golinko, and Arcasoy[11] reviewed 53 published cases of idiopathic hypercalcemia and found no reported cases of supravalvular aortic stenosis and peripheral pulmonary artery stenosis. Although a variety of lesions (edema to calcification) of the endothelium and media of the ascending aorta have been produced in the experimental animal by large doses of vitamin D,[12] the relationship of these lesions to the supravalvular aortic stenosis observed in patients with idiopathic hypercalcemia of infancy remains to be demonstrated. Supravalvular aortic stenosis and peripheral pulmonary artery stenosis can also occur as isolated findings, the latter defect being related to maternal rubella in pregnancy in some cases. The syndrome under discussion currently accounts for only a fraction of cases of supravalvular aortic stenosis and periph-

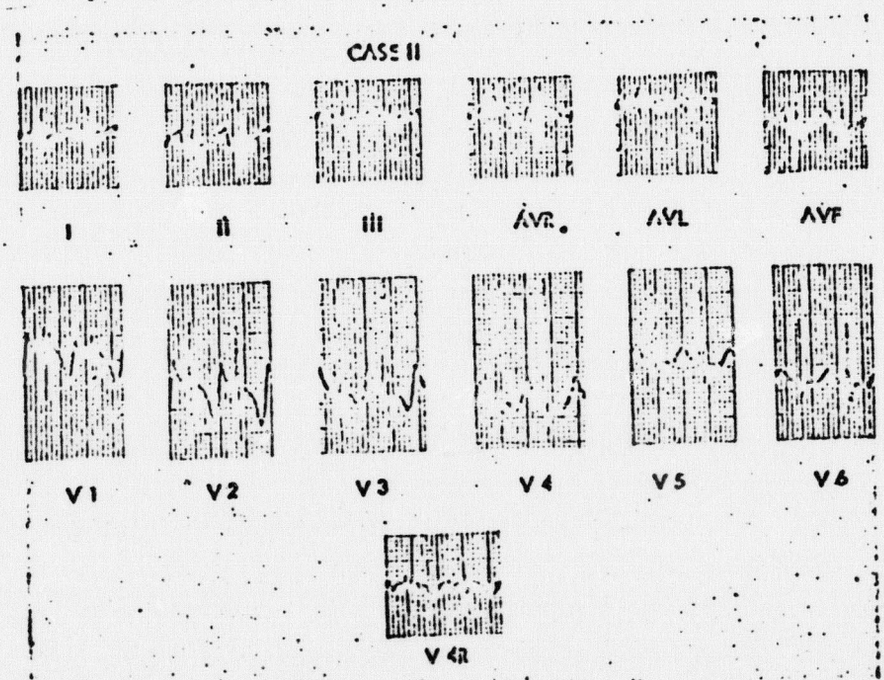


Fig. 10A. Case No. 2. Electrocardiogram at age 5 years. Sinus tachycardia, within normal limits.

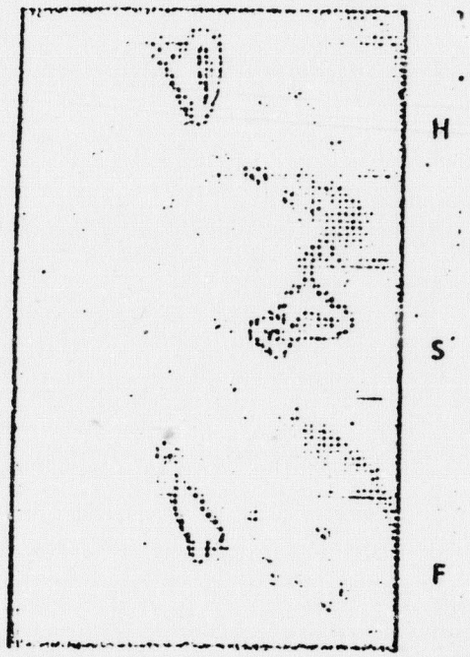


Fig. 10B. Vectorcardiogram using Schmitt system of electrode placement (SVEC III). Terminal forces of the QRSoT loop in the horizontal plane are directed posteriorly and to the right suggesting right ventricular preponderance. H, S, and F are all recorded at normal standardization ×5. (S = Left sagittal.)

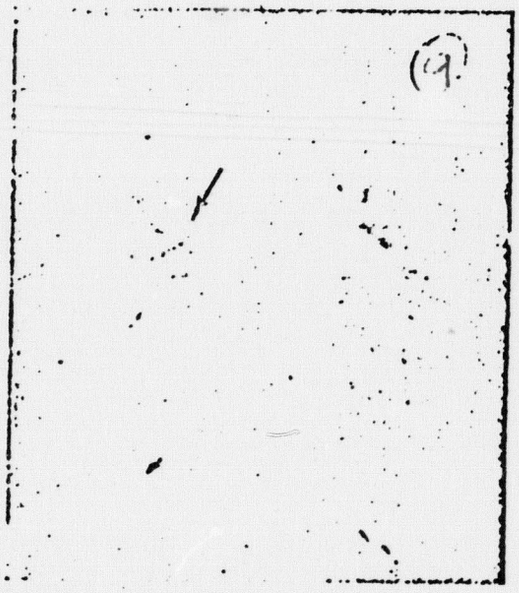

Fig. 11. Case No. 2. Frontal film of right ventriculogram demonstrating areas of mild stenosis and poststenotic dilatation of the right upper pulmonary artery. Arrow points to an area of stenosis.

eral pulmonary artery stenosis. Whether or not some cases lacking the typical facies may also be related to calcium or vitamin D disturbance is still undetermined.

The 2 cases in this report serve to illustrate the occurrence of supravalvular aortic stenosis and peripheral pulmonary artery stenosis as isolated entities in association with idiopathic hypercalcemia of infancy. Previous communications have stressed the combined occurrence of peripheral pulmonary artery stenosis and supravalvular aortic stenosis.[3, 7] Additional cases of isolated peripheral pulmonary artery stenosis in this syndrome can be expected as more cases of idiopathic hypercalcemia are studied. Both patients exhibited the peculiar hoarse, metallic voice and charming personality, as emphasized by Beuren and associates[3] to be characteristic for this syndrome.

In addition to the 2 cases reported here, we studied 2 other patients with supravalvular aortic stenosis, peculiar facies, and mental retardation. Peripheral pulmonary artery stenosis was demonstrated also in both of these patients. In each instance the facial characteristics and especially the peculiar hoarse metallic voice were similar. One patient also had a cleft lip and palate. Although no documentation of hypercalcemia was present in either of these cases during infancy, a review of the clinical history revealed some clinical features of hypercalcemia. Cardiac murmurs were recorded in only 5 of the 10 cases of idiopathic hypercalcemia studied at this institution and were judged to be significant only in the 2 cases described in this communication.

Genetic studies have been reported in patients with the syndrome of supravalvular aortic stenosis, mental retardation, and peculiar facies.[3, 13, 14] Beuren and associates[3, 14] found no chromosomal abnormalities in three patients with this syndrome. Merritt and associates[13] studied 8 unrelated families with this syndrome by pedigree analysis and chromosomal studies. In only one patient was

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there a chromosomal abnormality. This tool the form of a "46/47 mosaic with an extra chromosome resembling the 19-20 group." They concluded that there were 2 groups of patients with supravalvular aortic stenosis. The first group includes the "sporadic cases with the complete syndrome," and the second group includes "familial cases in which the trait is transmitted as an autosomal dominant with variable expression, lacking mental retardation and facial similarity." These two studies thus point to the absence of a specific chromosomal abnormality in this syndrome. There is also a preponderance of females among the reported cases with this syndrome (14 of 21).[3-6, 7]

The blood pressure has been observed to be higher in the right arm than in the left in the great majority of reported patients; this finding has been attributed, in some cases, to stenosis of the left subclavian artery. However, pressure differences also have been noted in patients with supravalvular aortic stenosis who had no apparent hypoplasia or stenosis of the left subclavian artery. In these cases, the pressure difference between the arms may be related to the jet caused by the stenosis. We have measured the pressure at the various regions of the aortic arch in one patient with supravalvular aortic stenosis during operation, and have noted that the pressure in the ascending aorta in the region of the innominate artery was higher than that measured in the region of the origin of the left subclavian artery. In the patient reported here, the pressure in the legs was the same as observed in the left arm.

The anatomic features of the types of supravalvular aortic stenosis represented in this syndrome are of considerable interest. Perou[13] has classified supravalvular aortic stenosis into three groups. In the first group, there is a circumferential ridge or shelf of media and intima protruding into the lumen immediately above the aortic orifice, producing the hourglass type of deformity. This group is considered the "true" form of supravalvular aortic stenosis. The second group includes cases with a discrete membrane obstructing the lumen. The third group includes the nonobstructing membranes, cords, or bands stretching across the aortic orifice. A review of the angiographic and pathologic reports of this syndrome reveals that the majority of cases have the hourglass type of deformity (Group 1). In only one instance was a supravalvular membrane reported.[1] Beuren and associates[3] have pointed out the finding of hypoplasia of the arch and descending aorta in this condition. The branches of the aortic arch may also be hypoplastic. Less commonly, the entire aorta distal to the obstruction is hypoplastic, as demonstrated in the present case. In the majority of cases, however, the ascending aorta became of normal caliber immediately above the stenotic zone. The hypoplasia of the aortic arch may form the basis for the previously emphasized "emptiness of the aortic knob" on the frontal roentgenogram in this condition.[3] A prominent ductus diverticulum is frequently seen with angiographic studies and has been considered specific for this cardiac anomaly.[3] We have observed prominence of the ductus diverticulum on aortograms in patients with other congenital cardiac malformations. The ductus diverticulum may well be accentuated in this condition by the hypoplasia of the aortic arch. The aortic sinuses are frequently dilated and the coronary arteries commonly are markedly dilated and tortuous. In the occasional case with dilatation of only one of the coronary arteries, deformity of the aortic sinus with obstruction of blood flow to the coronary ostium of the hypoplastic coronary artery may well be present. This has been reported earlier in cases of supravalvular aortic stenosis without mention of facies.[16, 17]

It is apparent that the relationship of idiopathic hypercalcemia of infancy to the syndrome of mental retardation, peculiar facies, peripheral pulmonary artery stenosis, and supravalvular aortic stenosis is still poorly understood. Further observation of patients with idiopathic hypercalcemia of infancy coupled with experimental animal studies on the effect of hypercalcemia and vitamin D on the developing fetus should be most helpful in this regard.

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## SUMMARY

The clinical findings in 2 patients with idiopathic hypercalcemia of infancy with associated congenital heart defects are described. The cardiac anomalies consisted of isolated supravalvular aortic stenosis in one patient and isolated peripheral pulmonary artery stenosis in the other. These data lend further support to the hypothesis that idiopathic hypercalcemia of infancy is intimately related to the syndrome of supravalvular aortic stenosis and/or peripheral pulmonary artery stenosis, mental retardation, and peculiar facies. Attention is drawn to the occurrence of peripheral pulmonary artery stenosis as an isolated cardiac anomaly in patients with this syndrome. In neither patient was there a history of excessive vitamin intake by the mother during pregnancy.


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# Vitamin D and the Supravalvar Aortic Stenosis Syndrome

## The Transplacental Effects of Vitamin D on the Aorta of the Rabbit

By William F. Friedman, M.D., and William C. Roberts, M.D.

RECENT REPORTS have indicated that idiopathic infantile hypercalcemia, a disease related to deranged vitamin D metabolism,[1-4] may be a feature of the nonfamilial, congenital supravalvar aortic stenosis syndrome.[5-8] Other manifestations of this syndrome include mental retardation, a peculiar "elfin" facies, narrowing of peripheral pulmonary and systemic arteries, strabismus, inguinal herniae, and dental abnormalities.[8] Congenital supravalvar aortic stenosis and peripheral pulmonary arterial stenosis also occur in a familial and a sporadic form unassociated with the other features of the syndrome.[10-13] It is not known if the multiple-system involvement in the supravalvar aortic stenosis syndrome is genetically determined or whether some or all of the features are related to a derangement of maternal or fetal vitamin D metabolism, or a combination of the two.

A paucity of information exists regarding the effects on the fetus of induced maternal hypervitaminosis D, and there appears to be no direct evidence for transplacental passage of vitamin D.[14-16] Studies concerning hypervitaminosis D in the nonpregnant animal emphasize the vascular toxicity of the vitamin.[17-23] Administration of excessive vitamin D to animals has been shown to produce dose-related vascular lesions, ranging from subendothelial edema to calcification, which are most pronounced in the ascending aorta just above the aortic sinuses. The pathogenesis of these vascular abnormalities is unclear.[19]

The present study was undertaken to determine whether vitamin D crosses the placenta, and to explore the relationship between hypervitaminosis D in the mother and the development of supravalvar aortic stenosis in the offspring. Blood levels of vitamin D from female rabbits that received excessive amounts of vitamin D and from their offspring were therefore determined, and the proximal aortae of these animals were examined anatomically.

### Methods

Adult, white, New Zealand rabbits were bred so that each female was mated with a different male. Eight females fed a stock diet* were designated as controls. In addition, three females were fed the stock diet especially prepared without vitamin D supplements, and these are referred to as "vitamin D-deficient mothers." Eight females were fed the stock diet* and, starting on the day after observed copulation and continuing until delivery, were given intramuscular vitamin D (activated ergosterol in cotton seed oil†) in divided doses every other day for a total dose of 1.5 million units. These animals are referred to as "mothers given vitamin D" (1.5 million units).

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*Stock diet: Protein, 18.0%; fat, 2.5 to 4.0%; fiber, 13.5%; ash, 9.0%; calcium, 1.3 to 1.6%; phosphorus, 0.3 to 0.5%; iodine, 0.003%; salt, 0.75 to 1.0%; carotene, 40 gamma/g; pantothenic acid, 8.4 g/lb; niacin, 15.75 mg/lb; thiamin, 2.0 mg/lb; riboflavin, 3.2 mg/lb; biotin, 0.09 mg/lb; vitamin C, 0.70 mg/lb; vitamin D, 768 mg/lb; vitamin E, 30 mg/lb; choline, 350 mg/lb.

†Hi-Deratol injectable, Brewer and Co., Inc., Worcester, Massachusetts.



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Three groups of five females each were fed the stock diet and in similar fashion were given intramuscular vitamin D for 30 days (the length of the rabbit's gestational period) beginning the day after observed copulation, for total amounts of 2.5, 3.5, and 4.5 million units, respectively.

Five control mothers and five given vitamin D (1.5 million units) were sacrificed with their progeny shortly after delivery. Prior to sacrifice blood was drawn from each mother for determination of calcium, phosphorus, alkaline phosphatase, cholesterol, total protein, albumin, lipoprotein phenotype,[24] and vitamin D. Similarly, blood for calcium, lipoprotein phenotype, and vitamin D determinations was obtained from each neonate. To obtain an adequate amount of serum for the vitamin D assay, samples were pooled from as many as three newborns from the same litter. The vitamin D bioassay[25] measured the response of rachitic rats to serum fed by stomach tube with the standard line test, as modified by Shue and associates.[26] The rachitogenic diet and methods described in the A.O.A.C. methods of analysis were employed.[27] Four or more rats were used for each assay.

Autopsy was performed on each of the five control and on each of the five mothers given vitamin D (1.5 million units) and on their offspring. The tissues were fixed in 10% Formalin, dehydrated in alcohol, embedded in paraffin, and sectioned serially at 6 $\mu$ intervals. The sections of heart and great arteries of each of the offspring were stained and examined histologically. In addition to hematoxylin and eosin, the Reinhart (for mucopolysaccharides), elastic van Gieson (for elastic tissue), Sudan black (for fat), and periodic acid-Schiff (for glycogen) stains were employed.

To evaluate anatomic changes in growing offspring given small daily quantities of vitamin D, three control mothers, three vitamin D-deficient mothers, and three mothers given vitamin D (1.5 million units) were not bled or sacrificed after delivering their offspring. After parturition the three vitamin D-deficient mothers were fed the stock diet and permitted to nurse their offspring. To avoid the consumption of large amounts of vitamin D from maternal milk, the offspring of the mothers given vitamin D (1.5 million units) were nursed by control mothers. The latter offspring as well as those of the controls were thereafter fed 250 units of vitamin D per day.* Whenever death occurred spontaneously in one of the offspring of the mothers given vitamin D (1.5 million units), a rabbit of the same age born to a control mother and to a vitamin D-deficient mother was sacrificed. All of the remaining offspring were sacrificed at 3 months of age. Gross and microscopic examinations of the hearts and great vessels were carried out in each rabbit.

*Crystalline vitamin $D_2$ in propylene glycol (Drisdol).

## Results

The results of the analyses of the serum of the mothers and offspring are presented in table 1. The levels of vitamin D were strikingly different in the various groups (table 1). The levels in the mothers given vitamin D (1.5 million units) and in their offspring were 7 and 9 times greater than the controls, respectively. Other than the levels of vitamin D there were no statistically significant differences in any of the other measurements between the groups of mothers (table 1). The calcium levels were somewhat lower and the phosphorus values somewhat higher in the mothers given vitamin D (1.5 million units) when compared to the controls. Significantly higher serum calcium levels were observed in the offspring of the mothers given vitamin D (1.5 million units) when compared to the controls. The high serum calcium levels noted in this study are in the same general range as those reported for the normal rabbit by others.[28] Cholesterol values were not significantly higher in the mothers given vitamin D (1.5 million units), and there were no qualitative differences in the electrophoretic lipoprotein phenotypes. The control mothers and the mothers given vitamin D (1.5 million units) had chylomicron, beta ($\beta$-), and alpha ($\alpha$-) lipoprotein bands of equal staining intensity. All of the offspring showed less intense $\beta$- and $\alpha$-lipoprotein bands than their parents, but there were no differences in staining intensity between the two groups of offspring.

Table 1

## Anatomic Observations

### Adult Females

There were no gross or microscopic abnormalities in the hearts or aortae of the control mothers. All of the females given 2.5, 3.5, and 4.5 million units of vitamin D died spontaneously within 65 days after their first injection of the vitamin, and all that con-

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Table 1

*Results of Analysis of Serum of the Mothers and Offspring*

| | Mothers | | Offspring | |
|---|---|---|---|---|
| | Controls | Given vitamin D (1.5 million units) | Controls | Mothers given vitamin D (1.5 million units) |
| Calcium (mEq/L) | 7.34 ± 0.24 (SD) | 6.88 ± 0.26 (SD) | 4.8 ± 0.11 (SD) | 5.55 ± 0.24 (SD) |
| Phosphorus (mg %) | 4.5 ± 0.75 | 5.7 ± 0.52 | $P < 0.05$ | |
| Alkaline phosphatase (King-Armstrong units) | 1.76 ± 0.53 | 1.15 ± 0.16 | | |
| Cholesterol (mg %) | 47.3 ± 3.4 | 56.3 ± 3.9 | | |
| Total protein (g %) | 4.3 ± 0.77 | 4.8 ± 0.33 | | |
| Albumin (g %) | 0.80 ± 0.27 | 0.87 ± 0.30 | | |
| Vitamin D assay (units/100 ml) | 310 ± 268 | 2150 ± 392 | 150 ± 138 | 1290 ± 359 |
| | $P < 0.001$ | | $P < 0.001$ | |

ceived either aborted during the first 12 days of pregnancy or delivered macerated fetuses. The entire aorta of each of these adult rabbits showed advanced changes, including irregular depressions in the intimal wall, focal calcium deposits, and foci of degeneration and necrosis of the aortic media. The aortae of the mothers given vitamin D (1.5 million units) showed similar but less striking changes. The alterations were most pronounced in the proximal portion of the aorta.

### Offspring

#### *Control Newborns Sacrificed after Delivery*

The aortic roots of the 23 control neonates were histologically normal. The normal invagination or plica at the upper margin of the sinuses of Valsalva[29, 30] was observed in some sections of each of these aortae, indicating that the plica does not extend around the entire inner circumference. The medial thickening that accounted for this invagination appeared moderately exaggerated (fig. 1 right) in five of these 23 aortae, but in none was it believed to be of sufficient proportion to narrow the aortic lumen significantly.

#### *Older Control Offspring*

With the exception of a ventricular septal defect in one, no other abnormalities of the heart or aorta were found in these 12 rabbits. The normal supravalvar aortic plica did not appear unusually prominent in any of these animals.

#### *Offspring of Vitamin D-Deficient Mothers*

No abnormalities were observed in these nine rabbits. The supravalvar aortic plica was present in each, but in none did it appear to be exaggerated.

#### *Newborns of Mothers Given Vitamin D (1.5 Million Units)*

The aortae of 14 of the 18 newborns in this group were normal, and 11 of these 14 aortae showed an exaggeration of the supravalvar plica similar to that observed in the five controls mentioned above (fig. 1 right). The higher incidence of this finding in this vitamin D group when compared to the controls is significant ($P < 0.001$). Four newborn rabbits,

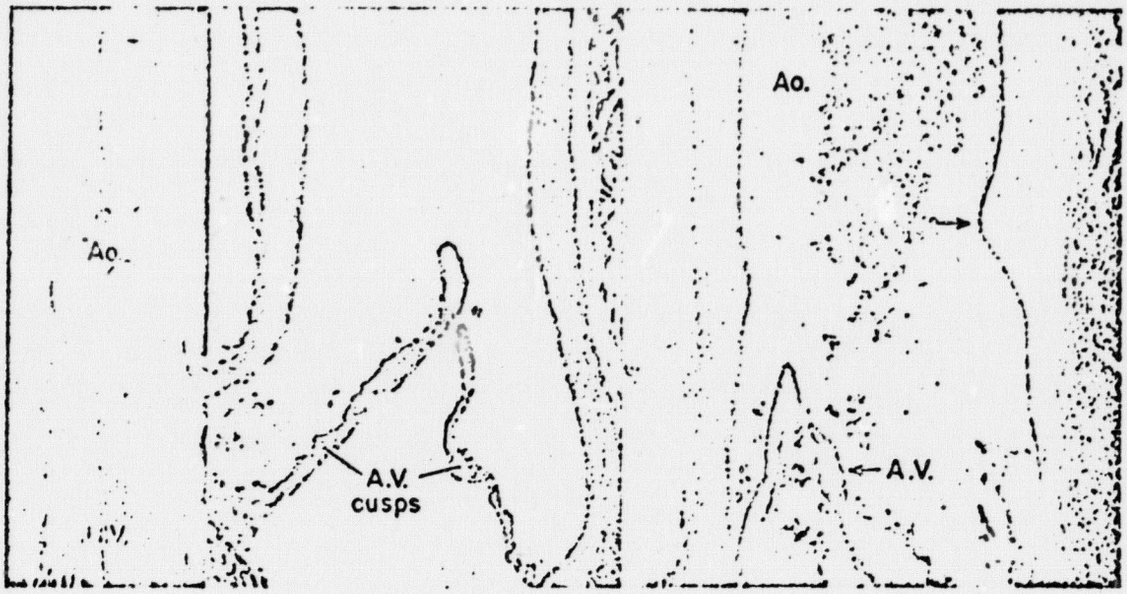


**Figure 1**

*Gross and microscopic appearance of aortic roots of control newborns. (Left) The left ventricle (L. V.) and aorta (Ao.) of a typical animal is shown. (Center) The aorta is smooth-walled beyond the sinuses of Valsalva. Aortic valve (A. V.); × 79. (Right) An exaggerated plica (arrow) at the superior margin of the sinuses of Valsalva is present in this animal. A similar degree of prominence of this structure was seen in five controls and 11 rabbits born to mothers given vitamin D (see text). Hematoxylin and eosin; × 39.*

each from a different litter, had abnormal aortae. In each animal there was a prominent annular protrusion at the superior margin of the sinuses of Valsalva resulting in significant narrowing of the luminal circumference at this level (fig. 2). The protrusion was caused entirely by proliferation of the media; the intima was normal. There was widening of the spaces between the elastic fibrils in the inner media. Stains for glycogen, fat, calcium, and mucopolysaccharides did not reveal abnormal deposits of these substances in the medial lesions.

*Older Offspring of Mothers Given Vitamin D (1.5 Million Units)*

Ten rabbits died spontaneously at 2 to 20 days of age. The cause of their deaths was not apparent at autopsy. There were no cardiac or aortic abnormalities in the four that lived less than 10 days and in two that died at 16 and 20 days of age, respectively. Supravalvar aortic abnormalities were noted in the four remaining rabbits, representing different litters. The aorta of a 7-day-old rabbit appeared normal on gross examination, but on microscopic examination an area of medial thickening and early degeneration just above the aortic sinuses was apparent. A 10-day-old rabbit had a nonobstructing fibrous band stretched across the lumen of the ascending aorta at the superior margin of the sinuses of Valsalva and a particularly prominent plica of the wall at this level. The aortae of the other two rabbits, a 20-day-old (fig. 3) and a 14-day-old (fig. 4), were severely narrowed in the region immediately above the sinuses of Valsalva by triangular-shaped protrusions or hillocks, and the aortic lumina distal to these sites were widened. These protrusions into the lumen resulted from localized thickening of the aortic media. In addition to an apparent increase in the elastic fibers and smooth muscle cells in the media, small foci of degeneration and round-

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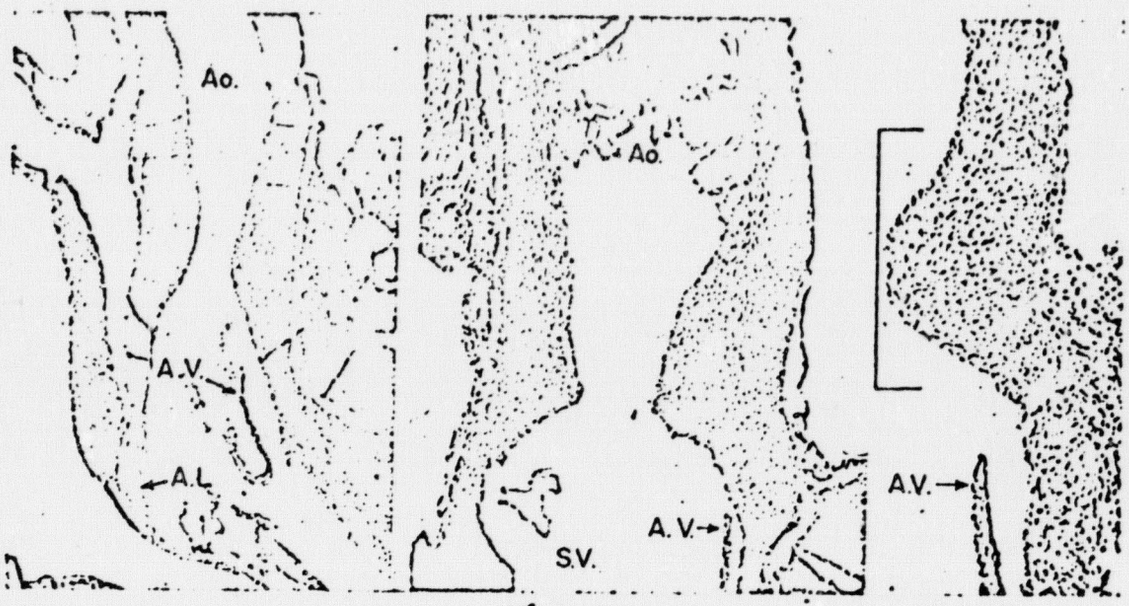


**Figure 2**

*The aortic roots of two newborns (left and center) whose mothers were given vitamin D (1.5 million units) show prominent annular protrusions impinging on the lumen at the superior margin of the sinuses of Valsalva. A higher magnification of the lesion (brackets) in a third newborn is shown on the right. The narrowing of the lumina results entirely from proliferation of the media. S. V., sinus of Valsalva; Ao., ascending aorta; A. V., aortic valve; A. L., anterior leaflet of mitral valve. Hematoxylin and eosin; × 39 (left); × 63 (center); × 97 (right).*

cell infiltration also were present. The arrangement of the elastic fibers and smooth muscle cells in the hillock produced an irregular pattern (fig. 3). A focal aneurysmal protrusion of the ascending aorta was observed in one animal (fig. 3). In the other animal, calcium deposits also were present in the media (fig. 4). The intima in each rabbit appeared normal, but the adventitia in one was focally thickened and invaginated into the media in a wedgelike fashion (fig. 3).

The remaining six rabbits in this group were sacrificed at 3 months of age. The changes in their aortae resembled quite closely the findings in the mothers given vitamin D (1.5 million units). The proximal aorta in these six animals showed generalized irregularities of the wall with degeneration and calcification of the media. The supravalvar area was not narrowed or disproportionately thickened, however, when compared to the rest of the ascending aorta.

## Discussion

Three specific anatomic types of supravalvar aortic stenosis (SAS) have been described in the human.[20, 21] The hour-glass type is the most common and is characterized by extreme thickening of the aortic media producing a constricting annular ridge. The membranous type is produced by a semicircular diaphragm with a small central opening stretched across the lumen of the aorta. The hypoplastic type is characterized by uniform hypoplasia of the ascending aorta. A fourth anomaly, of no functional significance, consists of a nonobstructing band or cord stretched across the lumen of the aorta at the level of aortic leaflets.

According to Perou,[20] the most common basic lesion is an angulation and exaggerated infolding of the wall with a thickened and focally disorganized medial layer capped by a zone of intimal thickening. The infolding may be shaped like a hillock or triangle

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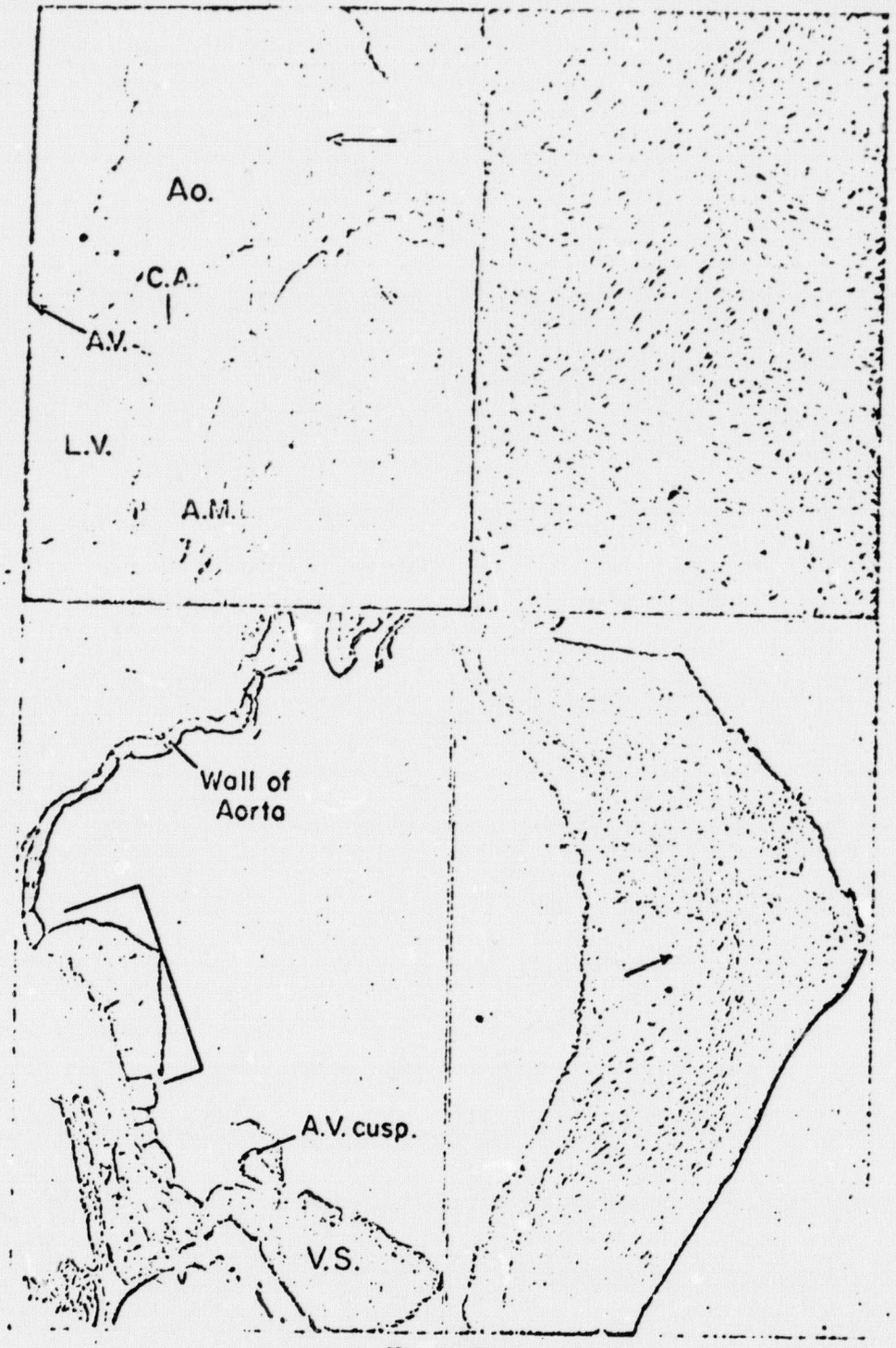


**Figure 3**

*Heart and aorta in a 20-day-old rabbit whose mother had received vitamin D. (Upper left)*



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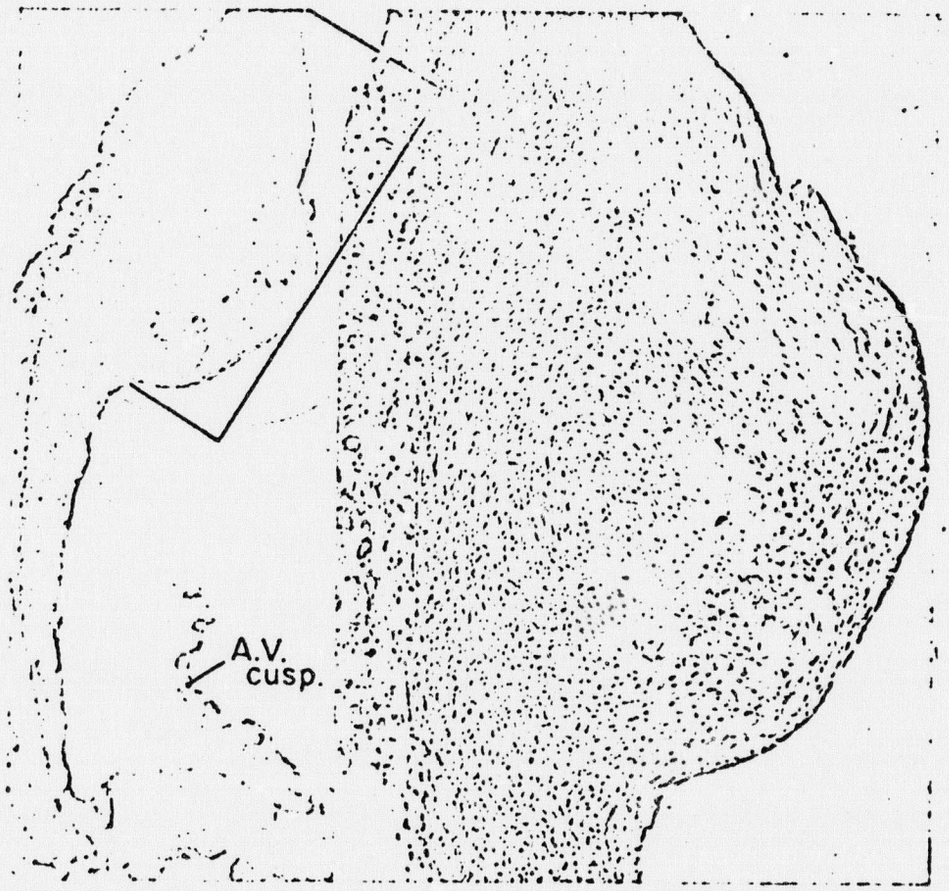


**Figure 4**

*The aortic root in a 14-day-old rabbit whose mother was given vitamin D. (Left) The wall of the aorta just above the sinuses of Valsalva is markedly thickened (brackets) and bulges into the lumen. A close-up of this area is shown in the photomicrograph on the right. Areas of necrosis and focal deposits of calcium are apparent. A. V., aortic valve. Hematoxylin and eosin; × 25 (left); × 160 (right).*

whose base is formed by the abnormal media and whose apex points toward the lumen. Foci of necrosis, round-cell infiltration, and calcification also have been noted in the hillock. Similar to the vascular changes in the animal given excessive vitamin D, the intrin-

**Figure 3 (continued)**

*The anterolateral wall of the left ventricle (L. V.) and left atrium has been removed, and the aorta (Ao.) opened. The lumen immediately above the aortic valve (A. V.) is narrowed and the aortic wall is thickened. The ostium of the right coronary artery (C. A.) is dilated. A focal protrusion or aneurysm (arrow) also is present in the ascending aorta. (Lower left) Section of wall of ascending aorta, aortic valve cusp (A. V.), and ventricular septum (V. S.). The prominent supravalvar aortic lesion (brackets) is triangular-shaped, with the apex pointing toward the lumen. The aortic valvar cusp is folded back toward the heart. Hematoxylin and eosin; × 7. (Upper right) Close-up view of the irregular pattern of the smooth muscle cells in the supravalvar area of thickening. Hematoxylin and eosin; × 107. (Lower right) View of another region of the supravalvar lesion. At this site the adventitia has invaginated in a wedgelike fashion (arrow) into the thickened media. Elastic van Gieson; × 25.*

sic pathology involves the inner half of the media.[17] In SAS the elastic fibers are broken and disorganized. There are focal increases in interstitial fibrous tissue and an irregular increase in smooth muscle. The adventitia is usually normal, but in one of Perou's patients it invaginated into the media in a wedgelike fashion.[29]

The aortic wall of many normal human newborns exhibits an incomplete transverse infolding or plica at the upper margin of the sinuses of Valsalva that is conspicuous in some normal aortae but practically absent in others.[29, 30] SAS is thought to be a developmental exaggeration of this normal structure.[29, 30] The present study demonstrates that this mild angulation and infolding of the aortic wall occurs in normal rabbits with varying degrees of prominence. Exaggerated prominence of the normal plica occurred without apparent narrowing of the lumen in a significantly higher percentage of rabbits born to mothers given vitamin D during pregnancy when compared to the controls. The aortae of the offspring whose mothers were fed a diet lacking vitamin D, however, also showed a supravalvar plica, albeit of lesser prominence, suggesting that the presence of the invagination does not depend solely on some action of vitamin D.

In the present study, eight offspring exposed *in utero* to high levels of antirachitic substance, presumably vitamin D, and to the maternal biochemical products of excessive administration of the vitamin revealed pathological abnormalities confined to the supravalvar aortic wall. In six instances the aortic lesions seriously impinged on the lumen and demonstrated essentially all of the histological features of SAS as seen in man.[29] The aneurysmal protrusion of the aorta of one rabbit has been observed in a similar location in SAS in man.[32] A nonobstructing delicate fibrous band crossing the proximal aorta was present in one rabbit. In another rabbit a medial lesion was microscopically evident although no gross abnormality was detected. The six offspring which were sacrificed at age 3 months showed the pathological changes associated with vasculotoxicity in the adult animal,[17, 33] although they received a cumulative oral dose of only 22,000 units of vitamin D from birth, leading one to question if they were predisposed to an increased tissue sensitivity to the toxic effects of the vitamin.

From this study it may be concluded that antirachitic substance crossed the hemochorial placenta of the rabbit and that the vascular toxicity of vitamin D can be transmitted across the placenta. There are definite similarities between SAS in the human and the lesions of the aortae in the offspring whose mothers received vitamin D. From these findings it seems reasonable to suggest that an *in utero* derangement in vitamin D metabolism on the part of mother or fetus or of both may be responsible for SAS, especially when the latter is associated with infantile hypercalcemia. It is necessary, however, to be cautious in drawing an analogy between the experimental animal model and the clinical disease. Because of the poorly understood and highly complex interaction between environmental and genetic factors that are involved in the genesis of human malformations, it must be stressed that our study does not supply a simple explanation for the syndrome of SAS and infantile hypercalcemia, but rather raises many questions. No emphasis has been placed on the prophylactic and therapeutic implications of the experimental findings. Further investigations will necessarily be stimulated by such considerations and hopefully will clarify the basic genetic, metabolic, and pathological mechanisms involved.

## Summary

Pregnant rabbits were given high doses of vitamin D to determine whether the vitamin crossed the placenta and to explore the relationship between maternal hypervitaminosis D and congenital supravalvar aortic stenosis. The blood levels of antirachitic substance in the mothers given vitamin D and their offspring were 7 and 9 times greater than in the control mothers and offspring, respectively, indicating that transplacental passage oc-

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curred. Serum calcium levels in the offspring whose mothers received vitamin D were significantly higher when compared to control values. A total of 14 abnormalities of the aorta were noted in the 34 offspring whose mothers received vitamin D. Aortic lesions that appeared similar anatomically to supravalvar aortic stenosis in man were noted in six rabbits. Also, one rabbit showed a supravalvar fibrous band and another had an abnormality of the proximal portion of the aorta observed only on microscopic examination. Six additional offspring at age 3 months showed generalized vitamin D vasculotoxicity, without supravalvar narrowing of the aorta, of an advanced type commonly seen in the adult animal given massive doses of the vitamin. Thirty-five control offspring and nine rabbits born to mothers on vitamin D-deficient diets showed no abnormalities of the aorta. The results suggest that an *in utero* derangement in vitamin D metabolism on the part of mother or fetus, or of both may be responsible for supravalvar aortic stenosis, especially when the latter is associated with infantile hypercalcemia. The questions raised by the experimental findings are emphasized.

### Acknowledgment

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### Gains from Serendipity

Readers who remember Bible stories will recall that Saul, the son of Kish, was sent forth to find his father's asses, which were lost. In the discouragement of his failures to find them he consulted one, Samuel, a seer. And Samuel told him not to set his mind on them for they had been found, but to know that he was chosen to rule over all the tribes of Israel. So it was announced, and the people shouted their approval. Thus modest Saul, who went out to seek lost asses, was rewarded by a kingdom. That is the earliest record of serendipity I am aware of.—Walter Bradford Cannon: *The Way of an Investigator*. New York, W. W. Norton & Co., 1945, p. 68; also in *Serendipity and the Three Princes*, Theodore G. Remer (Ed.). Norman, Oklahoma, University of Oklahoma Press, 1965, p. 176.

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corporation of orotate into RNA. Administration of insulin brought enzyme activities and RNA specific activities to normal.

These studies contribute valuable information about hormonal regulation of enzyme biosynthesis. They likewise extend our knowledge of biochemical processes of starvation and nutritional imbalance. The experimental approaches utilized are worthy of perusal for their possible application to other areas of nutritional investigation.

## CONGENITAL SUPRAVALVULAR AORTIC STENOSIS, IDIOPATHIC HYPERCALCEMIA, AND VITAMIN D

*An association has been recognized between idiopathic hypercalcemia and congenital supravalvular aortic stenosis. The latter can be induced in infant rabbits by administration of massive doses of vitamin D to the pregnant doe.*

Idiopathic hypercalcemia of infants has been recognized for the past 15 years as a cause of poor infant development, mental retardation, characteristic "elfin facies," strabismus, inguinal hernias, muscular hypotonia, osteosclerosis, and dental abnormalities (R. C. Lightwood, *Arch. Dis. Child.* 27, *502* (*1952*)). In addition to hypercalcemia, these children show elevations of blood urea nitrogen and cholesterol, renal dysfunction, and systemic hypertension. They can be subdivided into a benign group, which have a short self-limited course, and a more severe group with a grave, often fatal prognosis. The disease at first seemed to be virtually limited to the British Isles and Sweden, but recently reports have been coming from the Continent and the U.S.A. Its etiology is obscure, although an unusual sensitivity to vitamin D or a congenital defect in calcium or cholesterol metabolism has been postulated (*Nutrition Reviews* 14, *338* (*1956*)).

The elfin-like facies may reflect, in part, the low I.Q. and the unique dentition pattern. Both deciduous and permanent teeth may be incomplete in number, and incisors in particular may be absent or at least reduced in size. Not only is the shape of the teeth unique in round crowns, but there is also a marked dysgnathism. A search for chromosomal abnormalities has not been rewarding, and most documented cases of hypercalcemia have occurred in children from mothers receiving no vitamin supplements and pursuing no unusual dietary pattern.

Recently an association has been made between the occurrence of idiopathic hypercalcemia of infants and the subsequent development of supravalvular aortic stenosis (R. E. Garcia, W. F. Friedman, M. M. Kabaek, and R. D. Rowe, *New Engl. J. Med.* 271, *117* (*1964*)). There are three anatomic types of supravalvular aortic stenosis: a hypoplastic aorta, a diaphragmatic or membranous type of obstruction with a small central orifice, and, the most common, an hour-glass type: a constricting annular ridge of thickened aortic media. The latter type may occur sporadically, as well as familially, and may or may not be associated with other residual features of hypercalcemia. It was first observed by J. A. Black and R. E. Bonham-Carter (*Lancet* 2, *745* (*1963*)) to be associated with the characteristic facies, mental retardation, and dental deficiencies of children who may previously have been hypercalcemic. More recently, several cases of supravalvular aortic stenosis have been presented which had a documented idiopathic hypercalcemia in infancy (K. L. Jue, G. R. Noren, and R. C. Anderson, *J. Pediat.* 67, *1130* (*1965*); Garcia and coworkers, *loc. cit.*).

To investigate the possibility that this association could be due to a maternal vi-

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tamin D excess or a derangement in vitamin D metabolism, the following experiment was performed by Friedman and W. C. Roberts (*Circulation* 34, 77 (1966)). Eight control and 23 experimental female rabbits given large doses of vitamin D (activated ergosterol in cottonseed oil) were compared with regard to the extent to which vitamin D was transmitted across the placental barrier at the time of delivery of their litters, and to the presence of anatomical change in the ascending aorta both at delivery and at various times up to three months of age, at which time all remaining does and their offspring were sacrificed for autopsy study. Blood of does and neonates was examined for vitamin D by the rachitic rat biossay technique, and for calcium, phosphorus, alkaline phosphatase, cholesterol, total protein, albumin, and lipoprotein pattern.

There were eight does fed a control stock diet and three more fed an otherwise similar diet deficient in vitamin D throughout the period of observation. Four groups of five does each were given 1.5, 2.5, 3.5, or 4.5 million units of vitamin D intramuscularly every day from the date after observed copulation. All offspring then received 250 units per day of the vitamin in their diet until death or sacrifice.

At the time of delivery the mother rabbits receiving vitamin D and their offspring both showed significant elevations (sevenfold to eightfold) in blood levels of the anti-rachitic vitamin; and the offspring showed a somewhat higher blood calcium, but there was no significant difference in the other parameters between the control and treated groups.

There were no gross or microscopic abnormalities of the hearts or aortas of control mothers. The does receiving 2.5, 3.5, or 4.5 million units of anti-rachitic substance per day died spontaneously within about two months and either aborted or delivered macerated fetuses. Their aortas all showed advanced changes of medial degeneration with irregular depressions in the intimal wall, focal calcium deposits, and necrosis. These have been well-documented in the past (G. M. Hass, R. E. Trueheart, C. B. Taylor, and M. Stumpf, *Am. J. Path.* 34, 395 (1958)). The most interesting results were in the studies of the mothers receiving 1.5 million units per day, who showed changes somewhat milder than the above in their own aortas, and their offspring.

Even the normal aortas occasionally showed a normal invagination or plica at the upper margins of the sinuses of Valsalva. This plica never involved the entire circumference of the aorta, but was definitely exaggerated in five out of 23 newborns, in contrast to the older animals or the deficient neonates. Fourteen aortas out of 18 newborns of mothers receiving 1.5 million units of vitamin D per day were normal, although 11 showed this same exaggeration of the normal plica—a significant increase in incidence. The other four newborn, each from a different litter, had a prominent annular protrusion at this same supravalvular level which resulted in "significant narrowing of the luminal circumference." The defect was caused by a proliferation of the media covered by a normal intima.

Of the ten young rabbits dying between two and 20 days of age supravalvular abnormalities were noted in four, of the annular circumferential type in two. In the six animals finally sacrificed at three months, the aortas resembled those of their mothers (who had received vitamin D): there were generalized irregularities of the wall, with degeneration and calcification of the media. None had any localized supravalvular narrowing.

Thus, these workers have been able to produce experimentally in rabbits a congenital anomaly of the aorta which closely resembles the human defect. Furthermore, their experimental model involved a substantial derangement of the calcium-regulating vitamin, and it has gradually become established that, in the human, there is an

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association between supravalvular aortic stenosis and the idiopathic hypercalcemia of infants. It would be premature, however, to consider that this is another example of a simple exogenous factor, such as Thalidomide or the rubella virus, which produces a congenital vascular defect. Certain differences between the experimental model and the human disorder remain unexplained.

For example, excess intake of vitamin D by the mother has not been documented in a case of idiopathic hypercalcemia, much less supravalvular aortic stenosis. Although high blood levels of calcium, urea, and cholesterol are seen clinically, none was elevated in the experimental model. Thus, whether a dietary factor such as vitamin D is actually involved in the human situation seems quite unlikely, although it may still be postulated that there is some disturbance in vitamin D metabolism or enhanced sensitivity in response to it.

One wonders what role the parathyroid hormone and also calcium intake might play. In any event, it does seem clear that this type of supravalvular abnormality is an exaggeration of a normal fold of the aorta, that it is often preceded by hypercalcemia of the newborn, and that it can be occasionally induced in the rabbit fetus by administering to the mother massive doses of vitamin D, a substance which has long been known to cause changes in the arterial media of older animals.

## MULTIPLE FACTORS ALTERING RADIATION SENSITIVITY

*Survival studies of three strains of x-irradiated germfree and conventionally maintained mice indicate separate involvement of bacterial contamination and genetic factors in the determination of radiation sensitivity. Under some circumstances dietary treatment also affects radiation resistance.*

Investigation of the effects of various doses of x-radiation on many species, and also several strains of a single species, have shown that animals differ in the amount of radiation required to cause degenerative changes or death. Meticulous control must be used for strict comparability among studies (T. F. Dougherty, *Fed. Proc.* 20 (2), *part II, 3 (1961)*) and frequently unrecognized or uncontrollable differences in conditions make it difficult to evaluate results obtained from one laboratory to another or over a period of time in a single facility.

Further to substantiate earlier evidence of strain and environmental influences with respect to radiation resistance, H. E. Walburg, Jr., E. I. Mynatt, and D. M. Robie (*Rad. Res.* 27, *616 (1966)*) have studied the radiosensitivity of three strains of mice maintained under varying conditions.

Normally bred ICR and CF No. 1 and inbred RFM mice were maintained either conventionally or in plastic film isolators under germfree conditions. Periodic anaerobic and aerobic culture of feces and tissue for microorganisms, examination of intestine and skin for parasites, and serological examination for a number of viruses were conducted to assure a germfree environment, but no bacteriologic examination of conventional animals was reported. All animals were fed the same autoclaved diet and water ad libitum.

At ten to 12 weeks of age the germfree and conventional mice were irradiated in a sterile isolator with 500 to 1,000 R of x-irradiation at an exposure rate of about 100 R per minute. Actual exposures were monitored by a continuously recording exposure meter.

The 30 day mortality following these radiation doses ranged from less than 10 per cent to 100 per cent. Mortality curves were constructed by probit analysis of mortality data. The 50 per cent lethal dose for the 30 day period ($LD_{50(30)}$) was derived from these curves. When results for

# Possible Injury to the Cardiovascular System from Vitamin D

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THE INTEREST IN VITAMIN D as a possible source of injury to the cardiovascular system lies in the recent advances in our knowledge of supravalvular aortic stenosis. When, in 1958, Denie and Verheugt (1) reviewed the literature on supravalvular aortic stenosis, they found that 12 cases had been described, and they added 1 case of their own. After this, a number of such cases were recognized. In 1961, Wooley and associates (2) described the occurrence of supravalvular aortic stenosis in several members of one family. The existence of this so-called familial type has been confirmed by others and is now generally accepted as a clinical entity. The same year (1961) Williams, Barratt-Boyes, and Lowe (3) described a second type in which no familial aggregation was found but in which the supravalvular aortic stenosis was associated with mental retardation and a peculiar facies. These authors commented that the children looked "more like one another than like their own sisters and brothers." Moreover the facies were so distinctive that they suggested that the diagnosis might be made at sight. As so frequently occurs when a new clinical syndrome is recognized, a number of cases were immediately reported from various parts of the country and, indeed, from various parts of the world. In 1961, Beuren and coworkers (4) reported from Göttingen, West Germany, that peripheral pulmonary stenosis and an abnormality in the denture were also part of the clinical syndrome.

In 1963, Black and Bonham-Carter (5) recognized the similarity of the facies of those patients with supravalvular aortic stenosis to the facies of the children who had suffered from severe idiopathic hypercalcemia in infancy. These investigators then reviewed the autopsy material of infants who had died of the severe type of idiopathic hypercalcemia and found that in addition to the renal calcinosis these infants showed a wide variety of arterial stenoses, including renal artery stenoses and coarctation of the aorta; and although none had supravalvular aortic stenosis, abnormalities of the aortic valve were common among these infants. These observations immediately aroused the interest of pediatric cardiologists.

Idiopathic hypercalcemia has been known to pediatricians since Lightwood's (6) first report in 1952. This syndrome, too, is usually divided into two classes, the mild and the severe type of idiopathic hypercalcemia. The mild type is readily corrected by dietary measures. The severe type of idiopathic hypercalcemia is associated with anorexia, vomiting and failure to thrive, marked hypotonia, hypertension, a systolic heart murmur, renal insufficiency, and severe mental retardation. The high blood calcium level characteristic of hypercal-

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cemia suggested that it was related in some way to vitamin D intake or vitamin D metabolism (7). (ij. p 1952?)

During the next few years an increasing number of infants were recognized as suffering from this condition. Indeed, England suffered from a veritable epidemic of this disease. The epidemic occurred at a time when 1,000 units of vitamin D were being added to each quart of milk and vitamin D supplement was being added to many foodstuffs, such as cereals, bread, and flour. It was calculated that the majority of infants in Great Britain at that time received between 2,000 and 3,000 units of vitamin D/day. As soon as the vitamin D was taken out of the foodstuffs and the vitamin D content of milk was reduced to 400 units/qt, the outbreak of severe idiopathic hypercalcemia came to an abrupt end. Indeed, the decrease in the prevalence of idiopathic hypercalcemia was nearly as striking as the elimination of phocomelia in Germany after thalidomide was withdrawn from the market. The decrease in the severe form of idiopathic hypercalcemia that occurred with the reduction of the amount of vitamin D given to these infants is an incontrovertible fact, and it is a strong argument for the existence of some relation between the two conditions.

Idiopathic hypercalcemia has been extensively studied. The severe form is believed to be related to an abnormality in the metabolism of vitamin D of such a nature that these infants respond to a given dose of vitamin D with a greater rise and a more prolonged maintenance of a high level of vitamin D in the blood than occur in the average individual. Bongiovanni, Eberlein, and Jones (8) and Fellers and Schwartz (9) have considered this variation in metabolism to fulfill the criteria of "an inborn error" of metabolism; that is, the infants were born with an abnormality in the manner in which they metabolized vitamin D. This "inborn error" of metabolism is of such a nature that the infant is able to get a greater effect from a smaller amount of vitamin D than does the so-called "normal" individual. In other words, before the days of isolation of vitamin D, these infants could use the vitamin D that occurred in nature more effectively than could the so-called "normal" individual, and thus these individuals were less prone to rickets; now, because we can add unlimited amounts of vitamin D to our diet, we say those who can use it more effectively suffer from an "inborn error" of metabolism. The condition is more accurately described as an inborn "variant" in metabolism.

The important consideration in the present discussion is that some infants are born with an ability to metabolize vitamin D of such a nature that they can be seriously and severely injured by a dose of vitamin D that is apparently not injurious to other children. Moreover, this dose is approximately only eight times the usual amount required for normal growth and development. The figure eight times the usual amount is derived because a decrease from approximately 3,000 units/day to 400 units/day virtually eliminated the severe form of idiopathic hypercalcemia.

It is also of interest that Blizzard (10) has seen a family in which two children have suffered from iodiopathic hypercalcemia. When the mother of these two children was given a relatively high dose of vitamin D over a period of several weeks, she developed nervousness and a high blood calcium level, while the father showed no such reaction with the same dose of vitamin D over the same period of time. It is also of interest that, although these children have both shown a heart murmur from time to time, neither of the children has supravalvular aortic stenosis or any clinical evidence of a cardiac abnormality at the present time. Both children do show a rise in blood calcium when exposed to excessive sunlight and are therefore kept out of the full sun in the summer, and they are never given food to which

vitamin D has been added. In this instance the basic disturbance appears to be one of an abnormality in calcium metabolism.

To return to the problem of supravalvular aortic stenosis—in the spring of 1961 Garcia, Friedman, Kaback, and Rowe (11) reported an infant who was referred to the Cardiac Clinic of the Children's Medical and Surgical Center because of a cardiac murmur. On careful study this child was found to have a high blood calcium level, a high blood level of vitamin D, and supravalvular aortic stenosis. This, we believe, is the first reported case in which both hypercalcemia and supravalvular aortic stenosis have been reported.

In the summer of 1965 Black, Butler, and Schlesinger (12) reported that one of their original patients with a severe form of idiopathic hypercalcemia died of hypertension and renal failure at the age of 16 years. Autopsy showed renal calcinosis, massive left ventricular hypertrophy, and supravalvular aortic stenosis.

[Antia and associates (13) studied 14 children referred to our clinic with supravalvular aortic stenosis with both the familial type and the type associated with mental retardation. They found that these patients, regardless of the type of facies that they had, showed a wide spread in the range of their I.Q.s; many of them were slightly, although not severely, retarded, and those with a normal I.Q. showed curious variations in their response to certain mental tests. One patient with normal facies showed an abnormality of the denture suggestive of that seen in patients with supravalvular aortic stenosis and mental retardation. These findings suggested that the two types of supravalvular aortic stenosis represent different responses to the same underlying condition.]

Recently, Beuren (14) studied two infants who had been incorrectly diagnosed as having infantile tetany and had been given massive doses of vitamin D. Both infants at the age of 8 months had the full-blown picture of supravalvular aortic stenosis, peripheral pulmonary stenosis, and severe mental retardation. Beuren has started vitamin D loading studies and has advised me that not only do the patients with supravalvular aortic stenosis and mental retardation show an abnormal response to vitamin D, but also, those patients with the familial type of supravalvular aortic stenosis appear to be abnormally sensitive to vitamin D. Beuren suspects that patients with valvular aortic stenosis respond abnormally to vitamin D. This suggestion that aortic stenosis of the valvular type may be of similar or related origin does not surprise me because Bonham-Carter and Sulfice (15) have reported that many infants dying of idiopathic hypercalcemia showed abnormalities of the aortic valve. Exactly what determines whether an infant with a high blood calcium subsequently develops supravalvular aortic stenosis is certainly not clear. Nevertheless, all present evidence indicates that injury to the cardiovascular system occurs when there is an abnormally high blood calcium or an abnormality of vitamin D metabolism or the combination of these two factors. Under such a combination of circumstances the patient may develop what has generally been considered to be a congenital malformation of the heart.

This observation introduces a new aspect to the etiology of malformations. We are all well aware that nearly all grades of severity of a malformation exist in almost all types of malformations, as for example, a large and a small ductus or a mild and a severe stenosis; and furthermore we recognize that the most obstructive lesions become more severe over a period of years. Also, we recognize that the extreme of one malformation may merge into another; for example, an infant with tetralogy of Fallot and a pulmonary atresia, who survives the closure of the ductus arteriosus, has a functional truncus arteriosus. These observations concerning hypercalcemia and vi-

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tamin D indicate that at least in some instances the fetus can be injured and that such injury may result in a congenital malformation. Moreover, this injury that is associated with a disturbance in the metabolism of calcium and vitamin D causes both mental retardation and widespread injury to the vascular tree, which may result in supravalvular aortic stenosis, peripheral pulmonary stenosis, renal artery stenosis, possible aortic valvular stenosis, or perhaps even in some instances coarctation of the aorta.

During this past winter (1965 to 1966) Friedman and Roberts (16) approached the problem experimentally. They gave pregnant rabbits high doses of vitamin D to determine whether vitamin D crossed the placenta and to explore the relation between maternal hypervitaminosis and supravalvular aortic stenosis. Briefly, they found that the blood level of vitamin D in the pregnant rabbits given vitamin D was 18 times higher than that in the control rabbits and that the vitamin D assay of the offspring of the rabbits fed high doses of vitamin D was 9 times higher than that of the control. Among the 34 offspring whose mothers had received high doses of vitamin D, 14 showed abnormalities of the aorta. Moreover, 6 rabbits showed lesions that were anatomically similar to supravalvular aortic stenosis in man. In addition, 1 rabbit had a nonconstricting fibrous band above the aorta such as has been reported in man, and another had a microscopic abnormality in the proximal aorta; all of the controls were normal. In another experiment 6 offspring of mothers receiving high doses of vitamin D were given relatively small doses of vitamin D at 3 months of age. These rabbits developed generalized vitamin D toxicity of the advanced type seen in adults given massive doses of vitamin D, namely, generalized irregularities of the wall with degeneration and calcification. Friedman and Roberts emphasize the necessity for caution in drawing analogies between the experimental animal model and the clinical disease. Nevertheless, their experiments suggest that in certain animals —not necessarily all animals—an in utero derangement in vitamin D metabolism on the part of the mother or of the fetus or both may be responsible for supravalvular aortic stenosis, especially when the latter is associated with infantile hypercalcemia. In any event, these experiments showed that vitamin D can pass through the placenta and that abnormalities can occur in the offspring of the mothers who receive massive doses of vitamin D and that smaller doses at a later date can severely injure the aorta.

Obviously, experiments are needed to determine whether animals can be rendered hypersensitive to vitamin D, or only when mothers are fed excessive vitamin D may their offspring be rendered hypersensitive to vitamin D. Furthermore, their experiments also suggest that rabbits that have received an excessive amount of vitamin D in utero are susceptible to further injury if they are again fed vitamin D.

The question arises: how widespread is this phenomenon? At the present time three variations in the metabolism of vitamin D are known: [1] the "hypersensitive" response related to idiopathic hypercalcemia; [2] the normal or usual response; and [3] the children with vitamin D-resistant rickets. Are there just three points or is there a wide spectrum in the manner in which people metabolize vitamin D? Or is it all primarily related to disturbances in calcium metabolism? These observations open a tremendous field for study, and many of the problems lie in the realm of internal medicine.

For example, as one considers the various types of aortic stenosis, one wonders whether the calcific aortic stenosis of advancing years, that condition that has long defied pathologists as to whether it was congenital or rheumatic in origin, may not be of this nature, namely, the result of a

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combination of some genetic factor or increased sensitivity to vitamin D and the amount of sunlight and vitamin D that the individual received over a period of years.

In all probability there is some additional unknown factor of vital importance. The phenomenon of calciphylaxis that Selye (17) has studied may be of great significance. He has shown that animals may be given a dose of vitamin D, and subsequently at a critical time the animal is given another substance that acts as a challenger and produces calcification in various places. By varying the amount of vitamin D and the challenger Selye has produced calcification almost at will.

These observations open up many problems—I shall not speculate. Nevertheless, I do seriously wonder how great may be the variation in metabolism of calcium and of vitamin D and whether harm is being done by the widespread use of vitamin D in relatively high doses. Certainly we have virtually eliminated rickets, but some infants tolerate less than others and some infants need more than others; and perhaps some adults with a special genetic background may be injured.

Another interesting problem concerns the relation between calcium metabolism and hypercholesterolemia. In this connection, in 1963, Hooft, Vermassen, and Blancquaert (18) reported two cases. The first patient was a child who was known to have severe idiopathic hypercalcemia. He was treated with thyroxin and a low-calcium diet until 3 years of age; at 6 years of age he had a normal renal function, but he had hypercholesterolemia. The second was a patient with characteristic facies and a typical history of idiopathic hypercalcemia, marked mental retardation, and increase of density of the long bones, who at the age of 8 years had hypercholesterolemia and aortic stenosis. In this instance, the type of aortic stenosis is not known since the family of the latter patient refused to permit cardiac catheterization or angiocardiography. Be that as it may, the observation raises the question whether the problem is basically one of calcium metabolism or of vitamin D metabolism or the interaction of one upon the other, and what its relation is to cholesterol metabolism.

Whatever may be the outcome of these many problems, a new horizon has opened in the etiology of pathological conditions, both congenital and acquired, and we have further evidence of the late effects of early insults. My plea to you all is that, if large doses of vitamin D are not necessary and there is any possibility that they may do harm, do follow the old adage, "If you cannot do good, be sure not to do harm."


## Summario in Interlingua

Le possibilitate del lesionage del systema cardiovascular per vitamina D es suggestionate per le evidentia que un certe relation existe inter hypercalciemia idiopathic e le typo de stenosis aortic supravalvular que es associate con periphleric stenosis pulmonar, retardamento mental, e peculiaritates del facie.

Iste ultime characteristica esseva recognoscite como frappantemente simile al facie de juveniles qui ha supervivite a formas sever de hypercalciemia idiopathic. In plus, necropsias in infantes con hypercalciemia idiopathic ha revelate evidentia de un extense lesionage del systema cardiovascular in association con anormalitates del valvulas aortic. Un subjecto con hypercalciemia idiopathic qui moriva al etate de 16 annos habeva stenosis aortic supravalvular. Un infante con stenosis aortic supravalvular habeva un alte nivello sanguinee de calcium e monstrava un responsa a vitamina D simile a illo que occurre in subjectos con hypercalciemia idiopathic.

Hypercalciemia idiopathic es cognoscitemente relationate al quantitate de vitamina D ingerite e/o al metabolismo de vitamina D e es reguardate como un "error innate" in le metabolismo de vitamina D.

Le studios experimental effectuate per Friedman in conilios ha monstrate que vitamina D pote passar cis-trans le placenta, que grande doses de vitamina D alimentate al matre causava in le prole un anormalmente alte nivello de vitamina D a nato, e que septimanas plus tarde un dose medie de vitamina D causa un reac-

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tion toxic simile a illo que occurre post le alimentation de quantitates massive de vitamina D.

Iste observationes aperi nove vistas in le etiologia de malformationes e suggestiona fortemente que, in subjectos susceptibile, vitamina D pote esser nocive al systema cardiovascular ante e post nato. Il seque que meticulose attention es recommendabile in le uso de doses massive de vitamina D in patientes de omne etates.

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No. 13

## VITAMIN D
### Supravalvular Aortic Stenosis

It is now evident that some infants have the ability to metabolize vitamin D to such an extent that they can be seriously injured by a dose of vitamin D that is apparently not harmful to other children. The severe form of so-called idiopathic hypercalcemia seems to be related to this unusual ability to metabolize vitamin D. There is also evidence that hypercalcemia is, in turn, related to supravalvular aortic stenosis. In fact, many infants dying of idiopathic hypercalcemia show abnormalities of the aortic valve. Exactly what determines whether an infant with high blood-calcium levels will subsequently develop supravalvular aortic stenosis is not clear. However, all present evidence indicates that injury to the cardiovascular system occurs when there is a abnormally high blood calcium and/or abnormality of vitamin D metabolism. Under such conditions the patient may develop what has generally been considered to be a congenital malformation of the heart. The author concludes: "My plea to you all is that, if large doses of vitamin D are not necessary and there is any possibility that they may do harm, do follow the old adage, if you cannot do good, be sure not to do harm." -
Taussig (Baltimore, Md.), Ann. Int. Med. 65:1195 (Dec.), 1966

No. 14

## THORAZINE
### Pregnancy Tests

An 82-year-old woman developed jaundice after receiving 20 mg. Thorazine (chlorpromazine-SKF) daily for approximately 10 days. Of unique interest was the unusual and serendipitous finding of a positive immunological pregnancy test. Two weeks after the drug was withdrawn pregnancy tests on blood serum and urine were negative. The positive test was probably caused by excretory by-products of Thorazine in the urine or by Thorazine-induced changes in gonadotropins. Lactation and breast engorgement is known to occur as a side effect of Thorazine therapy (Clin-Alert No. 11, 1964). -
Paoletti et al. (Detroit, Mich.), Am. J. Med. Sci. 252:570 (Nov.), 1966

No. 15

## FURADANTIN
### Pulmonary Reaction

Pulmonary reactions due to Furadantin (nitrofurantoin-Eaton) have been previously reported (Clin-Alert No. 329, 1965; Clin-Alert No. 235 & 329, 1966). In these cases the patients were acutely ill. The present report is of special interest because it represents a subacute pleuropulmonary reaction secondary to Furandantin that manifested itself in a debilitating pulmonary illness. The patient had taken the drug for one year before symptoms of respiratory distress developed. The clinical course was characterized by marked dyspnea and orthopnea at rest, which were intensified by the slightest exertion. Tachypnea between 44 and 50 respirations per minute interfered with proper nutrition. Both lung fields were resonant and the breath sounds were emphysematous. Fine crepitant rales were scattered throughout both lung fields. All medication was withdrawn and prednisone therapy started. The response was dramatic. After one week the dyspnea and orthopnea ceased. Chest X rays revealed progressive clearing of infiltrates present on admission. Complete recovery ensued. -
Sollaccio et al. (New York, N.Y.), Ann. Int. Med. 65:1284 (Dec.), 1966

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carry a greater risk of complications from the drug itself.

Although this study demonstrated no serious complications or increased prevalence of infections in the treated group, the wide use of penicillin without proper indication has paralleled the generation of infections with hemolytic *Staph. aureus* resistant to penicillin in hospital populations.

One should be cautious before initiating prophylaxis with other antibiotics that may at present be considered to be effective against the staphylococcus, until there is clear-cut evidence that general surgical patients will be benefited by it.

TABLE 5. *Bacteriology in 33 Wound Infections.*

| Infecting Organism | Pure Culture | Mixed Culture | Totals |
|---|---|---|---|
| | No. of cases | No. of cases | |
| Hemolytic *Staph. aureus* | 22 | 6 | 28 |
| Streptococcus (gamma or beta hemolytic) | 1 | 3 | 4 |
| *Proteus vulgaris* | 2 | 3 | 5 |
| *Escherichia coli & Aerobacter aerogenes* | 0 | 4 | 4 |
| *Clostridium welchii* | 0 | 1 | 1 |

TABLE 6. *Bacteriology in 8 Cases of Pneumonia.*

| Infecting Organism | Pure Culture | Mixed Culture | Totals |
|---|---|---|---|
| | No. of cases | No. of cases | |
| Hemolytic *Staph. aureus* | 3 | 4 | 7 |
| Streptococcus (gamma or beta hemolytic) | 1 | 3 | 4 |
| *P. vulgaris* | 0 | 1 | 1 |
| *Esch. coli & A. aerogenes* | 0 | 1 | 1 |
| *Cl. welchii* | 0 | 0 | 0 |


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# ETIOLOGY OF THE SEVERE FORM OF IDIOPATHIC HYPERCALCEMIA OF INFANCY*

## A Defect in Vitamin D Metabolism


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WITHIN the past decade, a new syndrome has been described by Fanconi et al.[1] in infants showing retardation of growth. Mental retardation, renal dysfunction and osteosclerosis, in addition to dwarfism, characterize this clinical entity, and hypercalcemia, hypercalciuria and azotemia are the major biochemical abnormalities.

At about the same time, Lightwood[2,3] reported a large series of infants showing idiopathic hypercalcemia in whom failure to thrive, anorexia, vomiting and constipation were often associated with thirst and polyuria. Hypercalcemia and azotemia were also found in these infants, but osteosclerosis and mental retardation were not observed. In contrast to this mild, reversible form, only a few reports of the more severe disease have appeared.

Since few detailed metabolic observations have been made in this disease, the following cases and studies are reported – they show a consistent alteration in calcium and phosphorus metabolism and a relation of the abnormality to vitamin D metabolism.

## CASE REPORTS

The growth curves and laboratory data for the 3 cases are given in Figure 1 and Table 1.


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CASE 1.* A.S. (43-51-27), a female infant born on July 9, 1951, weighed 2.6 kg. and measured 52 cm. in length. She was given a regular whole-milk formula and a vitamin preparation,† 1 teaspoonful daily, until the age of 10 months. She took solid food from 3 to 6 months, but after 7 months she became a severe feeding problem, with intermittent vomiting, and intake actually averaged only 500 ml. of milk a day. Growth was retarded and at the age of 5 months she weighed 5.76 kg. Her 1st tooth erupted at 8 months. At the age of 15 months she was admitted to the hospital for evaluation of a left-sided facial paralysis of 1 week's duration. The family history was noncontributory. At this time she weighed 6.7 kg., and the head circumference was 43 cm. Initial laboratory studies showed a hemoglobin of 10.4 gm. per 100 ml.; urinalysis revealed a specific gravity of 1.012 and a trace to 1+ test for albumin. The blood nonprotein nitrogen was elevated at 74 mg. per 100 ml. Because she failed to sit up or support her weight and made no effort at vocalization, she was considered to be mentally retarded. X-ray study of the skull showed microcrania, with increased density of the bone.

She was readmitted to the hospital on January 9, 1956, for diagnostic studies. On physical examination the blood pressure was 110/60. She was small, appeared malnourished, weighed 6.9 kg., measured 74 cm. and had a head circumference of 43.5 cm. She was irritable and whined constantly. She followed objects with her eyes, but did not reach for them. A Grade 1 systolic murmur was heard in the 2d right costal interspace. The liver edge was palpated 1.5 cm. below the right costal margin. The remainder of the physical examination was not remarkable.

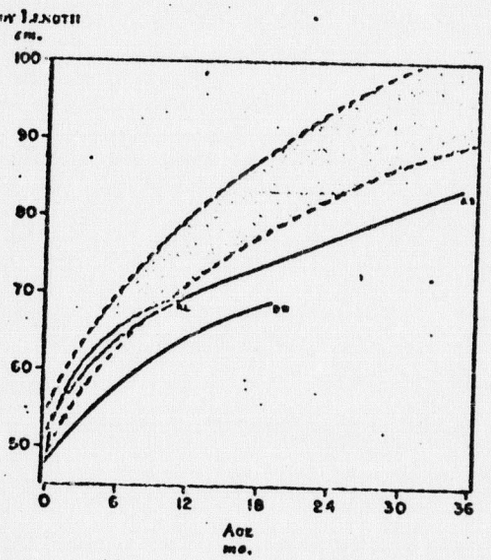


FIGURE 1. *Growth in Severe Hypercalcemia. The shaded area represents average 3d to 97th percentiles.*

Examination of the blood showed a hemoglobin of 10.0 gm. per 100 ml.; the maximum serum calcium was 3.5 millimols per liter, the alkaline phosphatase was normal, and the liver flocculation studies were negative. Urinary alpha-amino nitrogen was 13.3 mg. per 24 hours. X-ray study showed markedly increased density, with areas of irregular decreased calcification at the ends of the long bones. Nephrocalcinosis was evident in the abdominal film. The patient was discharged on a low intake of vitamin D, with sodium phytate, 0.5 gm. twice daily. In the interval before the 3d admission, in July, 1957, she began to eat better and was able to take some strained food; however, she had frequency of urination.

At the time of the third admission for balance and renal-function studies at the age of 36 months, she weighed 8.8 kg. and measured 81.5 cm. in length, and the head circumference was 45 cm. The blood pressure was 116/80. The remainder of the examination confirmed the marked degree of mental retardation. Laboratory studies showed a hemoglobin of 11.0 gm. per 100 ml., and urinalysis was unremarkable. Two 5-day balance collections for calcium and nitrogen were obtained, after which discrete inulin and para-aminohippurate (PAH) renal-clearance studies were done (Table 2).

CASE 2.‡ D.W. (44-41-71), a male infant, was born on August 21, 1955, after an uncomplicated pregnancy. He weighed 3.3 kg. and measured 43 cm. in length. He was given a whole-milk formula and vitamins,§ 0.6 ml. daily. At 3 months of age he weighed 4.8 kg. He smiled at 4 months. At 5 months, his physician noted that he was small for his age. He weighed 5.6 kg. at 6 months. After this his food intake decreased; he vomited occasionally and failed to grow. During a hospital admission at the age of 8 months an elevated blood urea nitrogen and an abnormal urinalysis were found. Bone age was determined to be at the 3-month level. He was then referred to the Children's Medical Center for evaluation. In the 3-week interval he received 15 mg. of thyroid daily.

On admission at the age of 9 months he was well proportioned, but small. He weighed 6.0 kg., his length was 63.5 cm., and his head was 40.5 cm. in circumference. The blood pressure was 140/86 with a 5-cm. cuff. He had a peculiar "elfin" facies, and a right-lower-facial-nerve paralysis was apparent at times. A Grade 2 systolic murmur was heard along the lower left sternal border. The remainder of the physical examination was negative although the patient did not sit or make efforts at locomotion. Urinalysis was abnormal. Anemia (hemoglobin of 8.7 gm. per 100 ml.), mild azotemia and hypercalcemia were found. Urine culture yielded several organisms on three occasions. X-ray studies showed a definite increase in density in the metaphyseal area of the long bones, at the base of the skull and in the pelvic and vertebral bones. An intravenous pyelogram showed poor excretion of the dye. The kidneys did not appear small, and no nephrocalcinosis was noted. Biopsies of rib, liver and kidney have been reported in detail elsewhere.* In particular, the kidney had an atrophic cortex and tubules. He was given sulfisoxazole for the urinary-tract infection and discharged on his regular intake.

At the age of 13 months he weighed 6.4 kg. and measured 65 cm., and the blood pressure was still elevated (150/60). He was taking approximately 900 ml. of whole milk daily and some solid foods. He was then started on sodium phytate, 1 gm. daily, and the vitamin D was omitted from his vitamin intake. Two months later he was started on a milk containing no added vitamin D as well, which was continued to the age of 19½ months.

When he was admitted to the hospital for special metabolic studies at this time, he weighed 6.7 kg. and measured 69 cm., and his head circumference was 41.5 cm. The blood pressure was 140/110. There had been no significant change in his condition. He continued to grow slowly. Both azotemia and hypercalcemia persisted. Two 5-day balance studies were obtained and discrete renal function was evaluated by the technic of inulin and PAH clearance with phosphate loading. Further x-ray studies showed marked progression of the osteosclerosis.

CASE 3. R.L. (46-26-79), a male infant, was born on January 26, 1957; he weighed 2.2 kg., and measured 48.3 cm. He took 800 to 1000 ml. of a whole-milk formula daily. In addition, he received 0.8 ml. of a standard vitamin preparation containing 1000 units of vitamin D per 0.6 ml. Development was normal during the 1st 3 months, when he weighed 5.4 kg. and measured 59.7 cm. At 4½ months he had 2 teeth.

During the next 2 months he failed to gain weight normally and did not seem to advance developmentally in learning or sitting. He ate poorly. Examination of the blood showed

*The radiologic features of this case have been reported previously.[4]

†Available as Vi-Daylin from Abbott Laboratories, North Chicago, Illinois.

‡Reported previously in a clinicopathological conference.[3]

§Available as Tri-Vi-Sol from Mead Johnson and Company, Evansville, Indiana.

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a normal hemoglobin and nonprotein nitrogen. A plain film of the abdomen disclosed increased density of bone, and an intravenous pyelogram indicated poor excretion of dye. He was admitted to the hospital on August 28 for evaluation. The family history was noncontributory. On admission he weighed 5.7 kg. and measured 67 cm. in length; his head circumference was 43 cm., and the blood pressure was 88/60. He appeared chronically ill, but physical examination was otherwise unremarkable. Examination of the blood showed a hemoglobin of 9.7 gm. per 100 ml. A random specimen of urine had a specific gravity of 1.009, and an overnight specimen for concentration had a specific gravity of 1.012. The maximum serum calcium was 3.3 millimols per liter. Creatinine clearance was depressed. X-ray study of the skull and long bones showed increased density, but not to a marked degree. He was given milk low in vitamin D, and other exogenous vitamin D preparations were discontinued. He continued to drink approximately 1 liter of milk per day at home and grew slowly. At the age of 11 months he weighed 11.8 kg. and measured 69.5 cm., and his head circumference was 47 cm.

## Methods

Balance studies were carried out on a metabolic ward. Intake was determined from the analysis of duplicate diets and of refusals. Vomitus was analyzed separately. Stool periods were marked with a standard 350-mg. carmine dye orally. Daily specimens of urine were collected under oil in an iced container and pooled for analysis in five-day periods. Blood

TABLE 1. *Laboratory Observations in Idiopathic Hypercalcemia.*

| Date | Age | Urine | | | | Blood | |
|---|---|---|---|---|---|---|---|
| | | Calcium | Magnesium | Phosphorus | Routine Tests | Hemoglobin | Nonprotein Nitrogen |
| | mo. | *millimols/24 hr.* | *millimols/24 hr.* | *millimols/24 hr.* | | *gm./100 ml.* | *mg./100 ml.* |
| Case 1 (born 7/9/54): | | | | | | | |
| 10/55 | 15 | | | | Specific gravity, 1.012; pH, 7.0; + test for albumin. | 10.4 | |
| 12/55 | 17 | | | | pH, 6.5; + test for albumin; *Escherichia coli.* | 9.5 | 75.4 |
| 1/56 | 18 | 0.73 | | 1.7 | pH, 5.0; + test for albumin; alpha-amino nitrogen, 13.3 mg./24 hr. | 10.0 | 60 |
| 4/56 | 21 | | | | | | 63.3 |
| 7/56 | 24 | (+ + + Sulkowitch test) | | | | | 67 |
| 10/56 | 27 | (+ + + Sulkowitch test) | | | pH, 5.5; negative test for albumin. | | 83 |
| 11/56 | 28 | | | | | | 101 |
| 2/57 | 31 | | | | | | 55 |
| 4/57 | 33 | 2.25 (+ + + Sulkowitch test) | 1.60 | 14.3 | Specific gravity, 1.005; pH, 6.5; + test for albumin. | | 69 |
| 7/57 | 36 | 1.28 | 0.70 | 8.4 | Specific gravity, 1.003; pH, 6.0; trace test for albumin; *Esch. coli.* | 11.0 | 74 |
| Case 2 (born 8/21/55): | | | | | | | |
| 6/56 | 9 | 0.90 (+ + + Sulkowitch test) | 0.42 | 6.2 | Specific gravity, 1.014; pH, 5.0; negative test for albumin; casts in sediment. | 9.3 | 61.4 |
| 9/56 | 13 | 1.96 (+ + + Sulkowitch test) | 0.90 | 7.8 | pH, 6.0; trace test for albumin; *Proteus vulgaris.* | 8.8 | 82 |
| 11/56 | 15 | | | | pH, 5.5; negative test for albumin; granular casts in sediment. | | 71 |
| 1/57 | 17 | 1.00 (+ + + Sulkowitch test) | 0.25 | 10.7 | pH, 5.0; trace test for albumin; clumps of white cells in sediment. | | 71.6 |
| 4/57 | 20 | 0.50 | 0.70 | 6.3 | pH, 5.5; trace test for albumin; *Esch. coli.* | 10.6 | 74 |
| Case 3 (born 1/26/57): | | | | | | | |
| 7/57 | 6 | | | | | 10.5 | 28 |
| 8/57 | 6½ | 0.94 (+ + + Sulkowitch test) | 0.74 | | Specific gravity, 1.012; pH, 6.6; negative test for albumin. | 9.7 | 29 |
| 10/57 | 8½ | 1.38 | | | | | 29 |
| 11/57 | 9½ | | | | | | 48 |
| 12/57 | 11 | | | | | | 66 |

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samples taken at the start of each period and at other times were allowed to clot for one hour, when serum was removed and frozen. Serum lipoprotein determinations were analyzed immediately.

Infant foods, formula, homogenized stool and urine were weighed in aliquots and digested with concentrated nitric acid and heat for forty minutes. The samples were brought to volume and filtered if necessary. For phosphorus and nitrogen analysis, original aliquots were digested separately with concentrated sulfuric acid. Sodium and potassium were determined by internal standard flame photometry,[6] chloride by a modified Volhard titration,[7,8] phosphorus by the Fiske and Subbarrow[9] technic and calcium and magnesium by initial oxalate precipitation followed by magnesium ammonium phosphate precipitation. The precipitates were dissolved in perchloric acid with heat, and the cation titrated with ethylenedinitrilo-tetraacetic acid with Cal-Red indicator[10] for calcium and eriochrome-black-T[11] for magnesium. Serum magnesium was determined by a modified titan yellow photometric technic,[12] cholesterol by the Schoenheimer-Sperry method,[13] serum total protein by a micro-Kjeldahl digestion technic,[14] serum vitamin A and carotene by a modified Blackfan and May technic,[15] and uric acid by a modification of

TABLE 1 *(Concluded).*

| DATE | SERUM | | | | | | |
|---|---|---|---|---|---|---|---|
| | CALCIUM | MAGNESIUM | PHOSPHORUS | TOTAL PROTEIN | CHOLESTEROL | ALKALINE PHOSPHATASE | OTHER |
| | *millimols/liter* | *millimols/liter* | *millimols/liter* | *gm./100 ml.* | *mg./100 ml.* | *Bodansky units* | |
| Case 1 (born 7/9/54): | | | | | | | |
| 10/55 | | | | | | | |
| 12/55 | | | | | | | |
| 1/56 | 2.8-3.7 | | 2.2 | 7.2 | 187 | 4.9-6.8 | pH, carbon dioxide content, chloride, sodium, potassium & alpha-amino nitrogen normal |
| 4/56 | 2.9 | | 2.1 | | | | |
| 7/56 | 2.6 | | 2.1 | 6.8 | | | |
| 10/56 | 2.9-3.6 | | 2.2 | 7.2 | | 9.3 | |
| 11/56 | 2.9 | | 2.5 | | | | |
| 2/57 | 2.7 | | 1.9 | | | | |
| 4/57 | 3.2 | | 2.3 | | | 6.2 | |
| 7/57 | 2.7-3.0 | 1.19 | 1.6 | 6.4 | 210 | | pH, carbon dioxide content, chloride, sodium & potassium normal |
| Case 2 (born 6/21/55): | | | | | | | |
| 6/56 | 2.8-3.2 | | 1.9 | 6.5 | 219 | 4.5-9.0 | Carbon dioxide, chloride, sodium & potassium normal |
| 9/56 | 3.0-3.3 | | 2.2 | 6.9 | | | |
| 11/56 | 3.4 | 1.00 | 2.6 | 6.1 | | | |
| 1/57 | 2.5 | | 2.4 | | 213 | 13.4 | |
| 4/57 | 2.4-3.2 | 1.03 | 1.6 | 6.3 | 200 | 8.0 | pH, carbon dioxide, chloride, sodium & potassium normal |
| Case 3 (born 1/26/57): | | | | | | | |
| 7/57 | | | | | | | |
| 8/57 | 2.9-3.3 | | 1.6 | 7.5 | 330 | | Carbon dioxide, 120 millimols/liter; pH, chloride, sodium & potassium normal. |
| 10/57 | 3.6 | | 1.7 | 6.2 | 260 | | |
| 11/57 | 3.3 | | 2.2 | 6.8 | 330 | | |
| 12/57 | 3.3 | | 2.2 | | 260 | | |

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the method of Natelson.[16] Urinary organic acid was determined by an electrometric titration using the Van Slyke and Palmer method,[17] titratable acidity by titration to serum pH with a pH meter with externally shielded electrodes, and ammonia by Conway's[18] microdiffusion technic.

Vitamin D was determined by the standard AOAC bioassay method[19] as follows: normal weanling Sprague-Dawley rats, twenty-one days of age, were placed on a rachitogenic diet containing 1.2 per cent calcium for twenty days. At the end of this time, severe rickets was manifest. The material for analysis was mixed with skim-milk powder, which had been ether extracted. This was fed in two doses on the first and third days. The diet was offered for a ten-day period, during which body weight did not decrease. The rats were then killed, and the tibias were dissected from the soft tissues. A longitudinal section of the proximal epiphysis was rinsed in water, immersed in 2 per cent silver nitrate for one minute and rinsed again in water. The specimen was exposed to daylight or an ultraviolet-light source for one to three minutes. The degree of calcification as evidenced by black staining without discoloration in the uncalcified areas was immediately graded 1 to 6; Grade 4 represented a solid line across the metaphysis. Seven rats, all of which had readable grading results, were considered adequate for each determination.

Clearance procedures were determined by both the endogenous creatinine and the inulin and PAH method. Creatinine was determined according to the procedure of Hare and Hare.[20] Discrete clearance measurements were performed after a standard priming dose of inulin and PAH, followed by a sustaining infusion of both in isotonic saline solution.[21,22] Urine was obtained from an inlying catheter and collected under oil with a sterile-water bladder wash. At least two bloods per each three clearance periods were obtained for extrapolation of serum values. A buffered phosphate solution for phosphate loading contained sodium phosphate, 11.36 gm. (80 millimols), and sodium biphosphate, 2.76 gm. (20 millimols) in 1000 ml. of solution. This solution was approximately isotonic (280 milliosmols per liter) and contained 3 mg. of phosphorus per milliliter. The pH was checked after autoclaving and before administration and was 7.3 to 7.4. A priming dose and sustaining solution were given.

TABLE 2. *Renal-Function Data.*

| Case No. | Age | Surface Area | Inulin Clearance | Creatinine Clearance | Para-amino Hippuric Acid Clearance | Filtration Fraction | Maximum Secretion of Para-amino Hippuric Acid |
|---|---|---|---|---|---|---|---|
| | mo. | m² | ml./min./m² | ml./min./m² | ml./min./m² | | mg./min./m² |
| 1 | 36 | 0.43 | 14.4 | — | 76.6 | 0.19 | 9.5 |
| 2 | 9 | 0.30 | — | 19.5 | — | — | — |
| | 19 | 0.34 | 16.7 | — | 66.2 | 0.25 | — |
| | 20 | 0.34 | — | 15.9 | — | — | — |
| 3 | 7 | 0.32 | — | 16.2 | — | — | — |
| Normal range | | 1.00 | 76.0 ± 15.0 | | 360.0 ± 70.0 | 0.21 ± 0.05 | 42.0 ± 10.0 |

## RESULTS

The 3 infants were normal at birth, but by the age of four or five months evidence of a generalized growth disturbance appeared (Fig. 1). Each child had been first referred to the hospital for failure to thrive. The diagnosis of hypercalcemia was not recognized immediately in Case 1. However, the subsequent radiologic findings were diagnostic. Both Case 2 and Case 3 were recognized initially from the x-ray studies, which indicated the abnormal bone density.

Laboratory data are presented in detail in Table 1. The serum calcium concentrations were elevated (2.75 to 3.65 millimols per liter whereas the normal range is 2.40 to 2.75 millimols per liter), although occasionally a normal value was found. Magnesium concentration in the serum was slightly elevated on a few determinations, which may have been related to the depressed renal function. Serum phosphorus was variable, but tended to be normal. During a period of progressive azotemia in Case 1 the serum phosphorus increased, but later returned to normal levels with her general improvement.

Cholesterol values were only occasionally elevated. Serum total protein determinations were normal. Serum total lipoprotein was normal in Case 1, 280 mg. per 100 ml., and Case 3, 571 mg. per 100 ml. (normal, up to 800 mg. per 100 ml.). Serum vitamin A was consistently elevated in all 3 patients (91 to 187 microgm. per 100 ml.) and serum carotenoids were elevated in Case 3 only.

Serum citrate was increased in 2 patients, being 3.5 mg. per 100 ml. in Case 2 at eighteen months and 5.0 mg. per 100 ml. in Case 3 at eight months (normal, 1.6 to 2.8 mg. per 100 ml.). Alkaline-phosphatase levels in the serum remained in the normal range throughout.

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The renal-function studies indicated significant impairment in all 3 infants (Table 2). Glomerular filtration was reduced to 20 to 25 per cent of normal. Renal plasma flow, determined in 2 of the patients by PAH clearance, was decreased to an equal degree, with a resultant normal filtration fraction. Tubular secretory function (PAH tubular maxima) in 1 patient (Case 1) was depressed to the same degree. During this study with a nonreabsorbable anion (PAH) load, potassium secretion was noted (the excreted to filtered ratios varied from 1.72 to 2.00).

An acid urine (pH of 5.03 to 6.62) was excreted by all the infants, and significant titratable acid and ammonia were found. Although maximal acidification was not evaluated after acid loading, an increase in titratable acidity was observed during phosphate loading. Urinary excretion of organic acid was normal, but urinary citrate was only 40 to 50 mg. per twenty-four hours (normal, 100 to 120 mg. per twenty-four hours) in each child. Excessive aminoaciduria was not found in 2 of the patients (Case 2, 9.2 mg., and Case 1, 13.3 mg. per day).

Phosphate excretion in Cases 1 and 2, determined during the clearance studies with inulin, is presented in Table 3. In both patients phosphate reabsorption varied from 66 to 90 millimols per 100 ml. of filtrate at normal serum phosphate levels. An acute phosphate load, which raised the serum phosphate from 1.5 to 2.3 millimols per liter, caused a twofold increase in phosphate reabsorption.

TABLE 3. *Renal Reabsorption of Phosphorus.**

| SUBJECT OR TEST | INULIN CLEARANCE | SERUM PHOSPHORUS | PHOSPHORUS REABSORPTION |
|---|---|---|---|
| | *ml./min./m²* | *millimols/liter* | *millimols/100 ml. of filtrate* |
| Adults[22] | 21-82 | 1.1 | 92 |
| | 11-20 | 1.1 | 56 |
| | 5-10 | 1.6 | 40 |
| Patients with hypercalcemia: | | | |
| Case 1 (36 mo. of age) | 15 | 1.5 | 90 |
| Case 2 (19 mo. of age) | 14 | 1.5 | 66 |
| | 18† | 2.3 | 122 |
| Normal infant (16 mo. of age)[24] | 58 | 1.8 | 137 |
| | 73† | 3.6 | 165 |
| 20 hr. after 600,000 units of vitamin D intramuscularly | | | |
| | 64 | 1.9 | 143 |
| | 61† | 3.9 | 208 |

*Reference data recalculated for purposes of comparison.
†During intravenous buffered phosphate loading.

Calcium excretion in the urine was elevated in all 3 infants and varied from 0.5 to 1.5 millimols per day. The calcium and nitrogen balance data are presented in Figure 2. In relation to the minimal nitrogen balance, which fluctuated insignificantly, the calcium balance was positive (13 and 18 per cent in Case 1 and 33 and 36 per cent of the intake in Case 2).

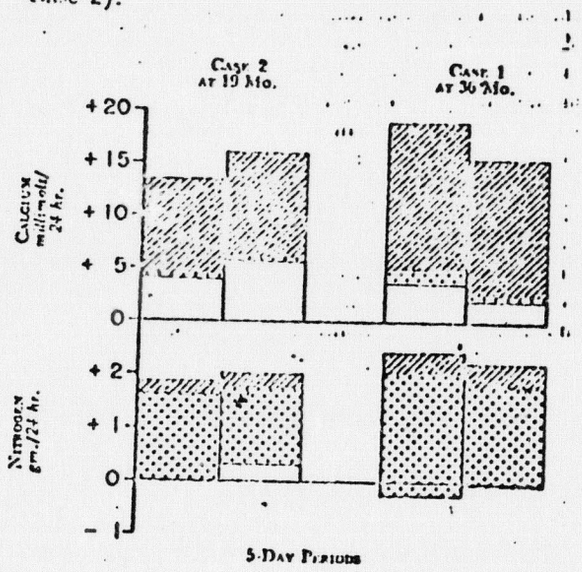


FIGURE 2. *Balance Data in Severe Hypercalcemia. Intake is plotted up from the baseline; stool (crosshatched area) and urinary (stippled area) excretion are plotted down from intake. A clear area represents positive balance; an area below the baseline represents negative balance.*

The results of the bioassay for serum vitamin D activity are presented in Table 4. The level of serum activity in 4 normal infants receiving standard multivitamin supplements varied from 100 to 200 units per 100 ml. of serum. In contrast, the levels in the 3 hypercalcemic infants were markedly elevated to twenty to thirty times the normal values. The serum of the hypercalcemic infants contained 1700 to 6000 units of vitamin D activity per 100 ml. These values are comparable to the results obtained in serum from 1 child with resistant rickets who received 62,500 units of vitamin D orally a day.

## DISCUSSION

Although an excessive vitamin D ingestion or an unusual sensitivity to this vitamin has been postulated as the cause of the mild form of idiopathic hypercalcemia of infancy,[7] no direct proof of this relation has been obtained. The high incidence in Great Britain, where over 200 cases were recognized in a two-year period, has diminished since excessive exogenous vitamin D intake has been curtailed there.[3] Previously, infants in Britain were estimated to receive as much as 4000 units daily, mainly as calciferol added to infant foods. An intake exceeding 1800 units daily has been shown by Jeans and Stearns[26] to retard optimal growth in young infants. The British Paedi-

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atric Association recommended a decrease in the vitamin D content of infant foods as a result of these findings.

Infants with the mild form of hypercalcemia do not have severe constitutional signs, including mental and growth retardation and osteosclerosis; moreover, the disease is usually self-limited and benign. Therapy of this form of the disease consists of removal of vitamin D from the diet, a reduction in calcium intake or the administration of cortisone, or all three. These cause the serum calcium to return to normal more promptly, with improvement in the clinical condition. Such treatment generally seems to be necessary for only a few weeks.

In contrast to the more frequently reported Lightwood or mild form of hypercalcemia is the limited occurrence of the severe or Fanconi type, of which more than 15 cases have been reported. This appears to be an unrelated entity, although there are features common to both. The cases reported here are strikingly similar to the cases of Fanconi and Schlesinger (Table 5).

The early history and growth data indicate that the 3 infants described above were normal at birth although no chemical and radiologic studies were available then. The exact time of onset of the disease is unknown, and the possibility of an onset *in utero* related to some maternal influence cannot be excluded. The earliest signs were nonspecific and related mainly to growth retardation. Only careful radiologic and chemical studies clarified the diagnosis.

Renal impairment, evident readily as azotemia, is one of the principal findings (Table 6) in the severe form of hypercalcemia. There was significant impairment in glomerular filtration, renal plasma flow and tubular secretory function. The symmetrical reduction to about a fourth of normal with a normal filtration fraction (glomerular filtration rate to renal plasma flow) and a normal effective tubular ratio (renal plasma flow to functional tubular tissue) indicates a loss of total nephron population. The renal biopsy in Case 2 at nine and a half months of age was consistent with these observations. Hypercalcemia per se may cause diminished renal function, which is reversible.[27] Since the hypercalcemia undoubtedly was present before diagnosis, the exact relation to the renal impairment found is not known. Certainly, considerable renal damage was present at the time of diagnosis at eighteen, nine and seven months of age in each child, as was evident from abnormal urinalyses, azotemia and diminished clearances. Renal infection was found in 2 of the infants (Cases 1 and 2) as a complicating event.

An interpretation of phosphate clearance in these infants is difficult because of the advanced renal impairment. The control values, as compared with those of normal infants on a surface-area basis at

TABLE 4. *Serum Activity of Substance Similar to Vitamin D* in Normal Children and Adults (Rachitic-Rat Bioassay).*

| Subject or Test | No. of Rats | Serum Aliquot | Activity | |
|---|---|---|---|---|
| | | *ml.* | *healing units* | *U.S.P. units/ 100 ml. of serum* |
| | 21 | — | 4.6 | — |
| Normal children: | | | | |
| R. (1 yr. of age) | 5 | 2.0 | 4.5 | 185 |
| N. (1 yr. of age) | 5 | 2.0 | 4.5 | 195 |
| McD. (2 yr. of age) | 3 | 2.0 | 5.0 | |
| | 3 | 3.0 | 5.3 | 184 |
| H. (2 yr. of age) | 3 | 2.0 | 3.9 | |
| | 3 | 3.0 | 5.0 | 172 |
| Children & adults[24] | | 1.5-4.0 | | 110 |

*Reference *U.S.P.* standard in oil, 0.1 microgm. of vitamin $D_3$ = 4 units.

TABLE 5. *Serum Activity of Substance Similar to Vitamin D in 3 Hypercalcemic Infants and a Patient with Resistant Rickets (Rachitic-Rat Bioassay).*

| Subject or Test | Age | No. of Rats | Serum Aliquot | Activity | |
|---|---|---|---|---|---|
| | *mo.* | | *ml.* | *healing units* | *U.S.P. units/ 100 ml. of serum* |
| Hypercalcemic infants: | | | | | |
| Case 1 | 33 | 7 | 0.05 | 1.8 | 3100 |
| | 36 | 7 | 0.10 | 1.4 | 1700 |
| | 42 | 7 | 0.10 | 3.1 | 2700 |
| Case 2 | 14 | 8 | 0.05 | 3.4 | 6000 |
| | 19 | 7 | 0.05 | 2.2 | 3600 |
| Case 3 | 7 | 7 | 0.10 | 2.3 | 2000 |
| Patient with resistant rickets: | | | | | |
| G.T. | 48 | 6 | 0.10 | 4.9 | 4300 |

TABLE 6. *Clinical Features[1] of Severe Hypercalcemia.*

| Features | Case 1 | Case 2 | Case 3 |
|---|---|---|---|
| Dwarfism & mental retardation (with convergent strabismus) | ± | ± | ± |
| Persistent hypercalcemia | + | + | + |
| Normal or elevated phosphatemia | + | + | + |
| Renal disturbances, albuminuria, azotemia & low clearances | + | + | + |
| Hypercalciuria (& hyperphosphaturia) | + | + | + |
| Osteosclerosis | + | + | + |
| Alkali reserve slightly lowered | ± | ± | ± |
| Cholesterol slightly elevated | – | + | + |
| Serum sodium & chloride normal | + | + | + |
| Asymptomatic heart disease | + | + | – |

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normal serum levels, were either normal or depressed. However, when corrected for the diminished filtered load (low glomerular filtration with normal serum concentrations), the tubular reabsorption was increased as compared to data from adults with similarly depressed function[23] (Table 3). The addition of a phosphate load (in Case 2) resulted in a twofold increase in reabsorption. This increase is similar in degree to that found by Klein and Gow[24] after parenteral vitamin D administration. Although the actual value for maximal tubular reabsorption ($T_{mp}$) as compared to values obtained during normal renal function is decreased, the ratio of $T_{mp}$ to load was increased in this infant.

Balance studies in 2 of the infants were carried out while they were given their usual dietary calcium intake. Since both infants were retarded and inactive, prolonged balance studies were feasible. Nitrogen retention was negligible in both infants. In contrast, calcium balance was markedly positive, especially considering the absence of growth. The degree of net absorption, which varied from 17 to 35 per cent of the intake, was unusual and undoubtedly contributed to the marked osteosclerosis present in these infants, even though hypercalciuria occurred. Hypercalciuria, which is an important feature of the syndrome, may be related to the hypercalcemia, although increased calcium excretion has been described with normal serum calcium concentrations. Dent has suggested that vitamin D may have a local action on the kidney tubule to promote calcium excretion.[25]

Although no consistent pattern in serum cholesterol was observed, an abnormality in lipoprotein metabolism has been suggested. Salt and Wolff[26] have described 2 infants with severe hypercalcemia in whom elevated lipoproteins were found. In 2 of the cases reported above, lipoproteins were separated in the serum by ultracentrifugation. In 1 infant (Case 1), at four years of age, a normal distribution pattern was obtained. However, in the other (Case 3), at fifteen months of age, a total value of 571 mg. per 100 ml. was found, with 261 mg. per 100 ml. in the beta-lipoprotein fraction ($S_f^{3-9}$) (normal, up to 270 mg. per 100 ml.). Forfar et al.[27] postulated an abnormality in cholesterol metabolism with the production of a substance active in vitamin D, although a defect in lipoprotein metabolism was not considered.

The vitamin A levels, which were elevated in all 3 infants, also suggest an abnormality in lipoprotein metabolism. The vitamin A intake was estimated to be 5000 units daily, a dosage that does not usually result in increased serum values. Krinsky, Cornwell and Oncley[21] recently demonstrated the transport of vitamin A and carotene in lipoprotein fractions of human serum. A defect in the rate of clearing of serum lipids by an altered lipoprotein metabolism has not been demonstrated, however, in this disease.

The elevated serum citrate levels found in 2 of the infants during the early phase of the disease may have been related to the action of vitamin D. Carlsson[28] has suggested that vitamin D results in dissolution rather than accretion of bone, possibly through citrate metabolism. Furthermore, citrate has been increased in serum and tissues (other than the liver) by vitamin D administration.[29] Urinary citrate was low rather than elevated; however, the severe renal impairment limits citrate excretion.[24] The apparent paradox between the action of vitamin D described above and the radiologic finding of increased bone density may be explained by the other factors, including solubility of calcium salts and parathyroid activity, which also influence bone formation. Without dynamic measurements of calcium metabolism, relative rates of accretion and dissolution cannot be considered in detail.

The metabolic data obtained in these infants is consistent with the presently known actions of vitamin D. That excessive serum vitamin D activity is of primary importance in this syndrome is evident from the bioassay measurements, which indicate a consistent and highly significant increased activity of vitamin D in the serum of each of the three infants. The exclusion of exogenous vitamin D had no effect on the clinical and chemical condition. Since vitamin D had been given in a usual dosage up to 1500 units daily until the time of diagnosis, the contribution of exogenous vitamin to the pathologic process cannot be excluded. However, exogenous vitamin D loads would not be expected to produce acute biochemical changes in the presence of such high serum activity. Furthermore, activity has been found in the serum of these infants as long as fourteen months after the removal of exogenous vitamin D from the diet. This is well beyond the period during which exogenous vitamin might persist normally.

The nature of this substance active in vitamin D is unknown. The possibility exists that this is not the naturally occurring vitamin $D_3$, but another sterol. At least 8 compounds other than vitamins $D_2$ and $D_3$ have antirachitic properties.[25] A cholesterol derivative, an estrogen-related substance or an abnormal adrenal hormone could represent the unknown factor with vitamin D activity. Recently, vitamin D has been shown to be in the alpha$_1$-globulin and alpha$_2$-globulin fraction of the serum proteins,[26] the lipoprotein fraction. Regardless of the exact nature of this substance, the elevated lipoprotein values found in this syndrome further suggest the possibility of a defect in the transport of this substance similar to vitamin D. Thus, the etiology of the severe form of idiopathic hypercalcemia of infancy appears to be related to a defect in the metabolism of such a substance.

## Summary and Conclusions

Three patients with the characteristic clinical and

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chemical findings of severe idiopathic hypercalcemia of infancy are described.

The principal features of this syndrome have been shown to simulate the physiologic actions of excess vitamin D on the growing child.

Serum vitamin D activity determined by the rachitic-rat bioassay technic was found to be twenty to thirty times that in normal infants. This suggests that a defect in the metabolism of vitamin D or related substances is the primary etiologic factor in this rare syndrome, leading one to include this disease in the rapidly growing list of inborn errors of metabolism, or molecular diseases.

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# INTUSSUSCEPTION IN INFANCY AND CHILDHOOD*

## An Analysis of Seventy-seven Cases Treated by Barium Enema

MARK M. RAVITCH, M.D.†

BALTIMORE

WITH a detailed analysis of 152 cases of intussusception seen at the Johns Hopkins Hospital, a report of 32 patients treated primarily by barium-enema reduction has been presented.[1] Since that time hydrostatic-pressure reduction of intussusception by barium enema under fluoroscopic control has been the treatment of choice in intussusception at the Johns Hopkins Hospital.[2] Between the 1950 report[1] and January 1, 1958, 47 additional cases of unequivocal intussusception were recognized at the Johns Hopkins Hospital. There are a number of additional cases in which the diagnosis of intussusception was

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# VITAMIN D AND CARDIOVASCULAR, RENAL, AND BRAIN DAMAGE IN INFANCY AND CHILDHOOD

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# VITAMIN D AND CARDIOVASCULAR, RENAL, AND BRAIN DAMAGE IN INFANCY AND CHILDHOOD

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## INTRODUCTION

There has been increasing notice taken in the literature of recent years of a presumed congenital abnormality characterized by supravalvular aortic stenosis, a peculiar facies and severe mental retardation. That an hereditary genetic defect may play a part in this syndrome has been suggested. The possibility that this syndrome may be induced by excess vitamin D during gestation has also been considered. This paper presents the possibility that this syndrome is an expression of hyper-reactivity to vitamin D that can be especially severe during early infancy. There is evidence that it may be the anatomic consequence of the disease known as hypercalcemia of infancy, which many investigators have found to develop in infants receiving doses of vitamin D that are only slightly to moderately above those considered prophylactic. This paper presents evidence that generalized arteriosclerosis of infancy may be the most severe manifestation of vitamin D toxicity in infants with marked susceptibility to vitamin D, and that renal acidosis may be a less severe expression of this sensitivity. There is evidence that recommended daily dosages of vitamin D may be toxic for some susceptible people, and that the potency of vitamin D is significantly greater in milk than in oil. As Taussig[1] has recently observed, the inborn "variant" in the metabolism of vitamin D that made some children less prone to rickets in the days before unlimited vitamin D supplementation of our foods is now the so-called "inborn error of metabolism" that may be responsible for vitamin D-induced injury to the cardiovascular, renal, and central nervous systems.

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## THE SUPRAVALVULAR AORTIC STENOSIS SYNDROME

Williams *et al.*[2] first called attention (in New Zealand in 1961) to the association of severe mental retardation and a peculiar facies with supravalvular aortic stenosis in young patients with retarded growth (see FIGURE 1). Upon reviewing the literature on similar cases, they discovered that in two of the studies, the patients were found at autopsy to have had fibrous myocarditis and myocardial atrophy.[3,4] Since they suspected a myocardial abnormality in one of their four patients, they suggested the possibility that myocardial degeneration might be another facet of this new syndrome. It is of interest that the patient reported by Burry[4] had also been described as being congenitally mentally defective. The same year (1961), Perou[5] reported detailed histological studies of the supravalvular stenotic areas of the aortas of a 13-year-old boy and of a 24-year-old man who had been in a State Hospital for mental retardation. In the first case, the child's records indicated a history of malnutrition and congenital heart disease at one year of age; the facies of the second case seems to bear some relationship to that described by Williams *et al.*[2] The patient was described as having large ears, high and narrow palate, and irregular carious teeth, an appearance quite similar to that reported recently by Rosenthal and Doyle[6] in a child with supravalvular aortic stenosis. These characteristics are selected here for note because of their resemblance to those seen in survivors of infantile hypercalcemia[7] (see FIGURE 2). Friedman[8] has suggested that excess vitamin D during gestation may be responsible for the abnormalities of the craniofacial complex, characteristic of both the supravalvular aortic syndrome and infantile hypercalcemia.[8]

The histological characteristics of the circular ridge and constriction at the upper margin of the sinuses of Valsalva, seen in the two cases reported by Perou, included slight intimal thickening, hyalinized fibrous tissue, fragmentation and disorientation of the elastica, and foci of necrosis and calcification. The myocardium of Perou's second patient showed patchy areas of fibrosis, and the kidneys were contracted and granular. Histological changes of the aorta had also been reported earlier by other pathologists who sectioned the stenotic portion of the aorta.[3,4,9,10] It was Perou's conclusion that this type of supravalvular aortic stenosis is unquestionably congenital.

Since then, additional investigators have reported similar patients with the aortic lesions, mental retardation and peculiar facies, the entire complex often described as a congenital anomaly.[6,11-18] However, Eberle and Beuren,[19] who had reported three patients with characteristics similar to those described by Williams a year later, attempted to detect chromosomal abnormalities in their patients, without success. Merritt *et al.*[20] however, did find a chromosomal abnormality in one patient with the full-blown syndrome, among eight supravalvular aortic stenotic patients studied. In four of the eight families, only the proband was affected. The remaining four families, with only the supravalvular stenosis, had 25 probably affected individuals. In a more recent study by Kurlander *et al.*[21] of 27 cases of supravalvular aortic stenosis, nine also had mental retardation and peculiar facies. Chromosomal studies, performed in five of these cases, were normal.

In 1963, Black and Bonham-Carter,[7] one of whom was a co-worker in the early study by Schlesinger *et al.*[22] of an infant with hypercalcemia, noted the similarity of the appearance at the age of 11 of a survivor of that syndrome[23] to that of the children with the Williams' triad (see FIGURES 2 & 3). They

FIGURE 1. (top) Four patients (bottom) Profiles of children in fron *al.* and Circulation.

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FIGURE 1. (top) Four patients with supravalvular aortic stenosis (courtesy of Williams). (bottom) Profiles of children in front row. (Reproduced by permission of Williams, J.C.P. *et al.* and Circulation.

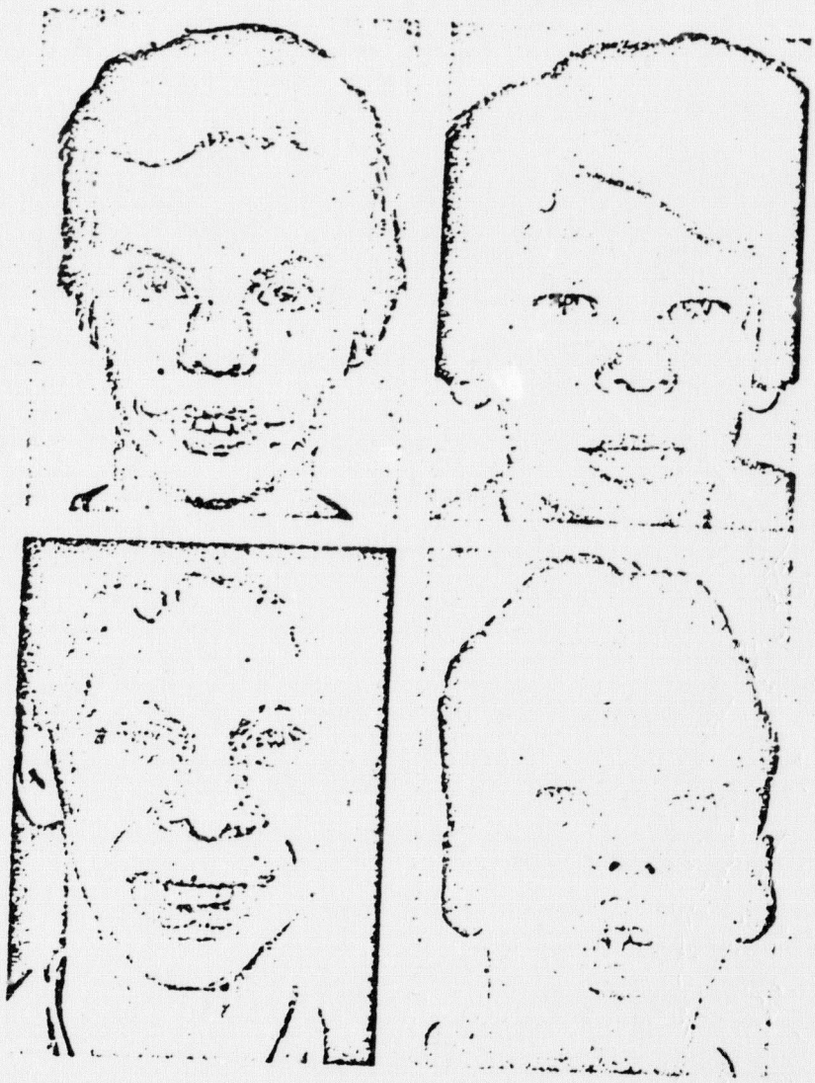

FIGURE 2. Survivors of infantile hypercalcemia. (Reproduced by permission of Black, J.A. and R.E.B. Bonham-Carter and Lancet.

presented five additional cases, all with clear histories of feeding difficulties and developmental abnormalities very similar to those seen in infants diagnosed definitively as having infantile hypercalcemia. They recently reported confirmation[24] at autopsy of supravalvular aortic stenosis in the child reported earlier as hypercalcemic[23] and noticed as resembling Williams' triad at the age of ten.[7] The child died at 16 years of age with renal failure, hypertension, and left



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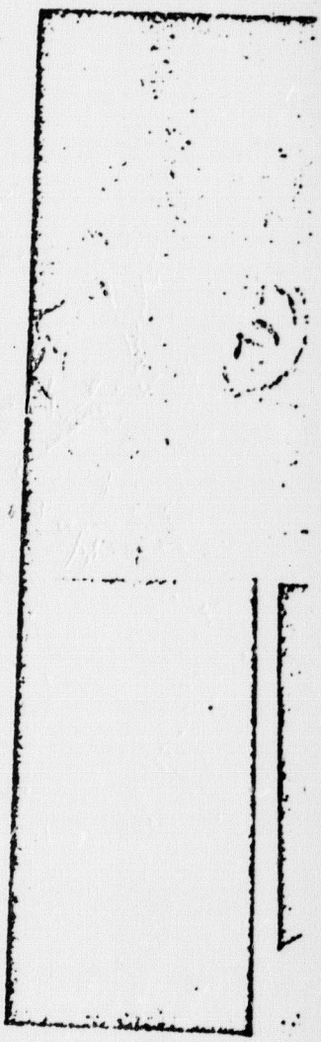

FIGURE 3. Patient with infa
years of age (bottom). ((A) Repr
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ventricular failure. The necropsy findings were small granular kidneys with numerous calcified areas, left ventricular hypertrophy, and a supravalvular aortic stenosis that had reduced the diameter of the aorta to 1 cm.[24]

Direct association of the Williams' syndrome with biochemically diagnosed hypercalcemia of infancy, was reported by Garcia *et al.*[25] Their patient was a

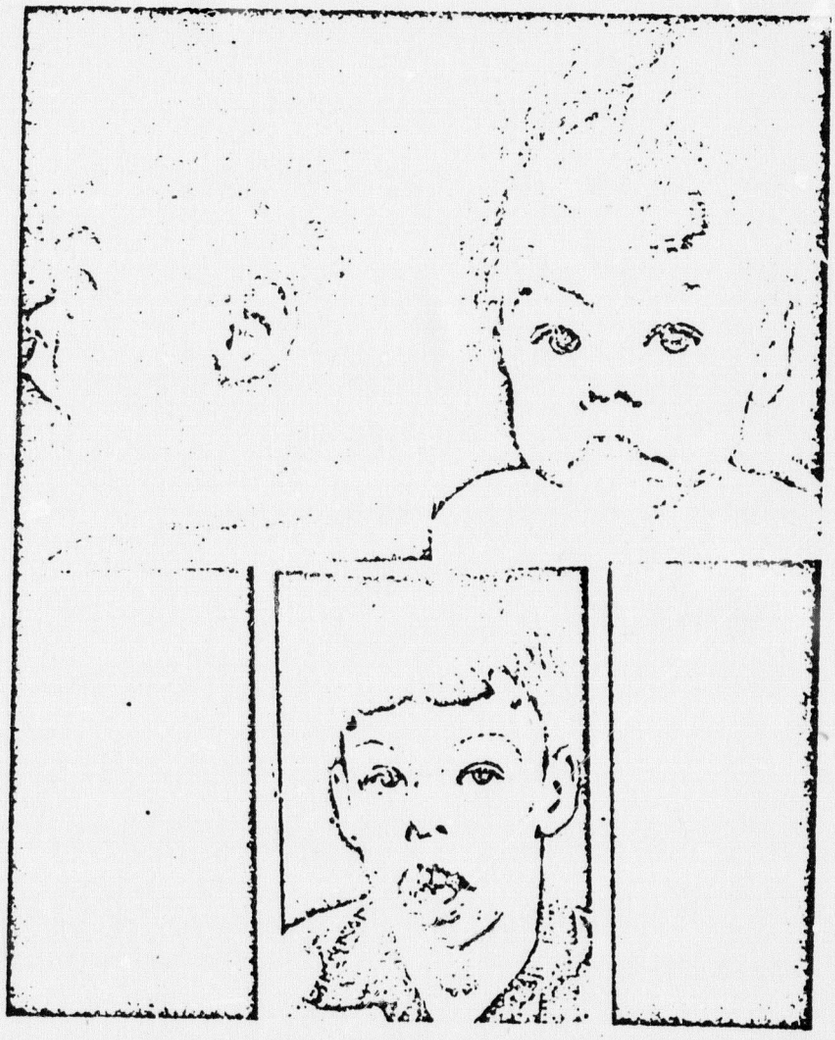

FIGURE 3. Patient with infantile hypercalcemia at 21 months of age (top) and at 11 years of age (bottom). ((A) Reproduced by permission of Schlesinger, B.E. *et al.* and Brit. Med. J., and (B) by permission of Black, J.A. and R.E.B. Bonham-Carter and Lancet.)

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FIGURE 4. Hypercalcemic infant with supravalvular aortic stenosis. (top) Note elfin faces, high prominent forehead, epicanthal folds, underdeveloped bridge of nose and mandible, and overhanging upper lip. (bottom) Roentgenogram of skull, pelvis and long bones and spine showing diffuse osteosclerosis and bands of increased density at metaphyses and at epiphyseal margins of vertebrae. (Reproduced by permission of Garcia, R.E. *et al.* and New Eng. J. Med.)

nine-month-old infant, who had a history of a normal neonatal course. At five months, cardiomegaly and murmur had been detected; subsequent to a herniorrhaphy at six months, retarded development was noticed. The child exhibited an elfin facies, (see FIGURE 4) and on roentgenographic examination, showed considerable sclerosis of the calvaria and base of the skull, with diffuse osteosclerosis of the long bones and vertebrae. Cardiac catheterization and cineangiocardiography revealed supravalvular aortic stenosis and mild stenosis at the origin of the left pulmonary artery. This case is of particular interest in that the classic Williams' syndrome was detected early, and was correlated with both hypercalcemia and a markedly elevated vitamin D blood level (1,540 units/100 ml, as compared with the usual value range of 60-400 units). In a recent review of idiopathic hypercalcemia, Fraser *et al.*[26] supported the concept that supravalvular aortic stenosis, mental retardation, and peculiar facies is the late normocalcemic stage of infantile hypercalcemia.

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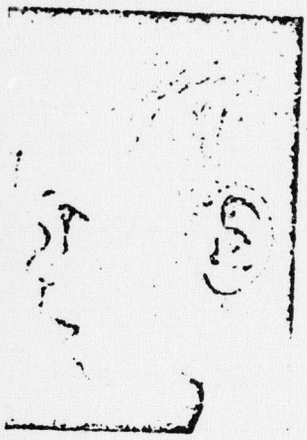

vular aortic stenosis. (top) Note elfin underdeveloped bridge of nose and ntgenogram of skull, pelvis and long nds of increased density at metaphyses d by permission of Garcia, R.E. *et al.*

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cardiac damage. One was a child with a less severe form of the disorder during infancy, involving anorexia, failure to gain, developmental retardation, and congenital heart disease (see FIGURE 5–A,B), and who showed marked improvement, with disappearance of all symptoms, signs and abnormal laboratory findings five years later. (FIGURE 5–C) The only significant treatment had been curtailment of vitamin D intake. Their second patient was a child who wasn't seen by this group until she was 20 months of age, and whose growth and development had been normal until she was one year old. This patient developed a harsh systolic murmur, renal damage, and mental retardation that was not reversible. Beuren *et al.*[28] reported nine additional children with the supravalvular aortic stenosis, most of whom also had pulmonic stenosis, and one of whom had a definite history of infantile hypercalcemia. (see FIGURE 6) More recently, Beuren *et al.*[29,30] reported a total of 55 children with supravalvular aortic stenosis in Germany, 40 of whom also had pulmonary stenoses. In this series, 23 had the typical facies of hypercalcemia of infancy and mental retardation. In many of these cases, clear histories of marked overdosage with vitamin D during infancy could be elicited; the mothers had also been given vitamin D prenatally. In the 14 children with supravalvular aortic stenosis reported by Antia and associates,[31] there was a wide spread in the range of their I.Q.'s, many of them showing only slight retardation, and others with normal I.Q.'s showing curious variations in responses to mental states.[1] One patient with normal facies had abnormal dentition suggestive of the syndrome in which aortic stenosis and mental retardation co-exist. Myers and Willis[18] have also reported the broad clinical spectrum of this disease. They have found that the supravalvular aortic lesion occurs in the absence of intellectual impairment and elfin facies almost twice as commonly as in the classic syndrome and tends to occur in families.

With the similarity in the two syndromes having been established, many investigators have commented on the possibility of a direct relationship in their reports of cases of supravalvular aortic stenosis associated with the "hypercalcemic facies" and mental retardation.[1,7,11,13,18,26,29-37] Taussig[1] has suggested that the two types of supravalvular aortic stenosis syndrome–that associated with, and that without, the characteristic facies and severe mental retardation–may represent different responses to the same underlying condition. Bonham-Carter and Sutcliffe[34] have called attention to a concomitant syndrome in which multiple arterial stenoses occur at the bifurcation of arteries, both in the systemic and pulmonary circulation. Since in infantile hypercalcemia the blood cholesterol is also high, they have postulated that atheromatous change at the stress points of bifurcation might be responsible for the stenotic changes. Friedman[35] reported that the Williams syndrome is relatively common, and that its association with infantile hypercalcemia may be missed. Beuren *et al.*[29,30] have commented on the frequency of this syndrome in Germany, where supplementation with high dosage of vitamin D is common. In a personal communication to Taussig,[1] Beuren voiced his suspicion that patients with supravalvular aortic stenosis respond abnormally to vitamin D. Friedman[35] has stressed the importance of early diagnosis because of the possibility of arresting, or possibly even reversing, the lesions by instituting appropriate therapy. Taussig[36] has published a provocative article, discussing the possibility that some relationship exists between the two conditions. She suggested that the inborn variation in man's ability to metabolize vitamin D may be responsible for the valvular changes seen in these conditions. The increase in blood cholesterol often seen in hypervitaminosis D, further suggests that such variation in

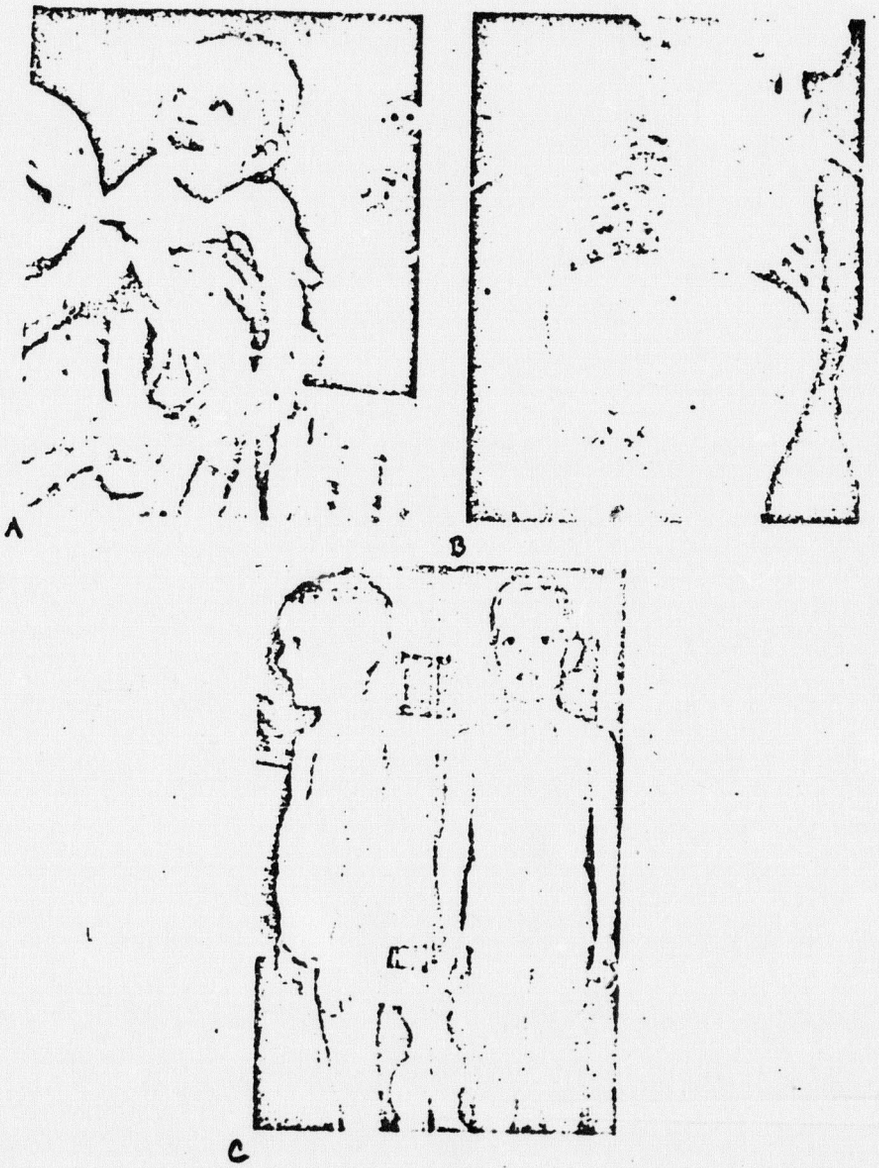


FIGURE 5. Hypercalcemic patient, who recovered on curtailment of intake of vitamin D.

A. Hypercalcemic infant: note malnutrition, poor development; low position of pinnas.
B. Roentgenogram, showing cardiac enlargement; "coeur en sabot" configuration.
C. Patient, five years later, demonstrating alert appearance, good muscular development.
(Reproduced by permission of Bauman, A. & C.G. Bauman and N.Y. State J. Med.)

FIGURE 6. Nine patients with
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## IDIOPATHIC HYPERCAL

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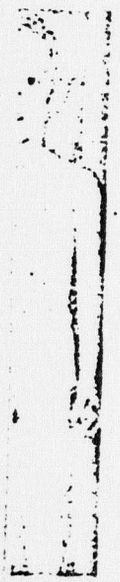

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FIGURE 6. Nine patients with supravalvular aortic stenosis. (Reproduced by permission of Beuren, A.J., C. Schulze, P. Eberle, D. Harmjanz & J. Apitz and Circulation Am. J. Cardiol.)

susceptibility to vitamin D may possibly be related to the far commoner vascular lesions associated with abnormal cholesterol metabolism. Her most recent article on the subject[1] presents a review of several of the published papers on this syndrome and includes comments on the similarity in the appearance of the children with supravalvular aortic stenosis to those with idiopathic hypercalcemia.

## IDIOPATHIC HYPERCALCEMIA, RENAL ACIDOSIS, AND VITAMIN D

### *Hypercalcemia of Infancy and Vitamin D*

The similarity of the syndrome comprising supravalvular aortic stenosis, mental retardation, and peculiar facies to that seen in survivors of hypercalcemia of infancy calls for a careful examination of not only the pathological picture,

but also the epidemiological background and the personal histories of the patients reported, to the extent that retrospective evaluation of the published data is possible. Reference should be made to Black's review[38] of the relationship of vitamin D to idiopathic hypercalcemia, and to the similarities of the clinical pathology caused by overdosage with vitamin D to that of the hypercalcemia syndrome.

The full complex of chronic hypercalcemia was first described in 1952 by Schlesinger and colleagues[22] and reported briefly by Lightwood[39] in England, and in detail by Fanconi and Girardet[40] in Switzerland. Each report dealt with a patient whose history indicated an intake of vitamin D that was not considered excessive (approximately 1,400 and 2,000 units after the first month of life.) Feeding difficulties, persistent vomiting, constipation, and failure to thrive or gain in weight characterized the early signs, with hypotonia and renal impairment seen in all three infants. Schlesinger's and Fanconi's patients also exhibited early electrocardiographic changes, and Schlesinger's patient had a harsh systolic murmur at six weeks. The patient reported by Lightwood had been referred to him because the symptoms suggested renal acidosis, a diagnosis that he excluded because of the normal plasma chloride, bicarbonate and inorganic phosphorus and because of the acidity of the urine. Each child had hypercalcemia and urea retention. Schlesinger's report included a follow-up to the age of three. The child's failure to develop normally was manifested by the age of five months. The retardation, associated with hypercholesterolism, at first suggested the possibility of hypothyroidism, and treatment with thyroid extract was attempted, without success. By two years of age, there was definite renal impairment, hypertension, and sclerosis of bone. There appeared to be no further progression of the disease from the age of two, but at three the picture was of a mentally retarded dwarf, with defective renal function, hypertension, and a systolic murmur. The similarity of the clinical picture, at the age of two, to hypervitaminosis D led the investigators to omit vitamin D from the diet from that time on. The failure of this deletion to change the biochemical picture or to alter the clinical status led the investigators to question their original impression that the condition may have been due to hypersensitivity to vitamin D.

Analysis of the many case reports on hypercalcemia of infancy reveals that the characteristics can be divided into early, or mild and apparently reversible signs, and the later irreversible changes of the severe form of the disease. Both the mild and irreversible forms start in the early weeks or months of life with symptoms of fretfulness, anorexia, vomiting, constipation, polydipsia, polyuria, hypotonia, and cessation or marked slowing of growth and of weight gain. At this stage, blood chemistry changes include hypercalcemia (usually over 12 mg/100 ml), azotemia, and often elevated blood cholesterol (primarily the free form). Blood inorganic phosphorus may be normal or slightly elevated, and alkaline phosphatase readings are generally low. Hypercalciuria and white cells in the urine are often detected. Recurrent infection is common, the disease often becoming overt after an acute severe infection.

Several infants, detected by blood chemical studies at that stage, have been put on a low calcium diet, delivering no vitamin D.[25-27,43-56] They exhibited fairly prompt relief of vomiting and anorexia, relief of constipation somewhat later, but persistence of elevated calcium and NPN levels for several months. Weight gain, and improvement in disposition and in muscle tone, have also been seen on such corrective diets. Corticosteroids have proven useful in inducing clinical improvement in infants with more severe manifestations.[26,42,50-56] Hypercalcemia and decreased renal function improved,[41,43,44,48,50,



50-56,59,60] as did cardiac function[26,27,41,45,46] in a few cases. The mental retardation, however, was irreversible. Apparently the longer the delay in diagnosis, the more severe was the physical damage. Hypertension and systolic murmur (often shown to have been due to supravalvular aortic stenosis) were seen, and renal damage became more severe with fixed gravity of urine, albuminuria, casts, hematuria, and signs of increasing renal insufficiency. Increased bone density, detectable on x-ray, developed. Craniostenosis and osteosclerosis, especially of the base of the skull, and, to a lesser extent, of the long bones and vertebral column, were frequently seen. In addition to retardation of growth, severe mental retardation became manifest in these infants. The infants are characterized by an "elfin" facies that is considered typical of the severe hypercalcemia syndrome. (see FIGURES 3–A, 4, 5–A, 7-9)[24,25,27,51,61,62] In later childhood, their appearance is characterized by a wide slack mouth, severe malocclusion and caries, prominent upper lip, underdeveloped mandible, depressed bridge of nose, widely set eyes, sometimes a convergent strabismus, epicanthic folds and low-set, prominent ears (FIGURES 2, 3–B).[7,23,24] This facies is indistinguishable from that seen in the "congenital" supravalvular aortic stenosis syndrome (FIGURES 1,6).[2,28]

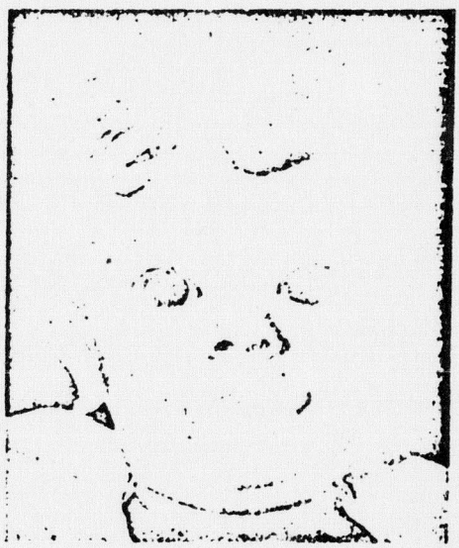

FIGURE 7. "Elfin" facies in idiopathic hypercalcemia. Note thin delicate ears, depressed nasal bridge, small mandible and high prominent forehead. (Reproduced by permission of David, N.J. *et al.* and Am. J. Med.)

FIGURE 8. Typical facies of infantile hypercalcemia. (Reproduced by permission of O'Brien, et al. and J. Am. Med. Assoc.)



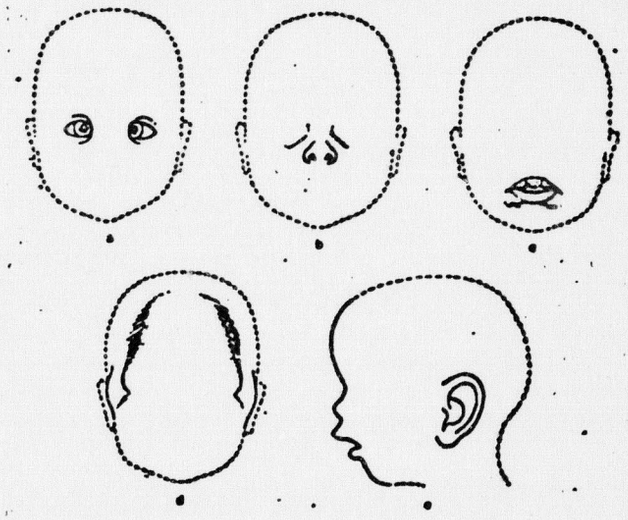

FIGURE 9. Components of the facies of infantile hypercalcemia. (Reproduced by permission of Joseph, M.C., & D. Parrott and Arch. of Diseases in Childhood.)

In order to determine whether the mild or simple form of infantile hypercalcemia does, as has been said, result in complete recovery once the infant is taken off vitamin D and put on low-calcium diet, Mitchell[61] followed the courses of 18 infants, diagnosed as having simple hypercalcemia in Scotland from 1953 through 1956, for three to six years. Four of these infants died, and autopsy disclosed nephrocalcinosis.[63] One was lost to follow-up at eight months, four months after having been put on a low-calcium milk preparation. Of the remaining 13 children, most showed slight delay in sitting up and walking, but all were sitting without aid by 12 months, and all had taken the first unaided step by 21 months. All but one seemed to have average mental development; the three who had had cardiac murmurs during the acute phase had no detectable cardiac abnormality at their last examination. Tests of renal function revealed no significant abnormality, and satisfactory growth progress was made. In all cases, the abnormal biochemical findings originally present, including hypercalcemia, depressed alkaline phosphatase, and elevated plasma cholesterol, had become essentially normal. On the other hand, Coleman,[64] who expressed concern at the persistence of infantile hypercalcemia in Scotland (13 patients admitted to hospital in 1962-1963), despite the lowered vitamin D allowance as food additives, reported electrocardiographic changes in 12 of those 13 infants. These changes, which he had reported earlier in 14 out of 24 children

admitted to a medical unit in Glasgow,[66] are characterized by an abnormal shape of the ST-T complex. These changes outlasted the hypercalcemic phase of the disease and suggested to this investigator that they may reflect left ventricular myocardial lesions.

Correlation of the extremely high incidence of "idiopathic" hypercalcemia of infancy in England in the years 1953-1957 with the excessive fortification with vitamin D of National Dried Milk and other Welfare and proprietary foods suggests that Schlesinger and colleagues'[22] original impression that hypersensitivity to vitamin D may have been an etiological factor may have been correct. Search of the literature has elicited over 25 articles dealing with case reports on over 80 infants who developed the syndrome during that period of time,[7,23,24,38,39,41,43,46,49,52,56,57,60,63-76] That probably few infants so affected have been reported in print was clearly indicated by the 1956 report of the British Pediatric Association that 204 cases of hypercalcemia were reported by June, 1955 to 196 consultant pediatricians in the United Kingdom.[73] When the feeding difficulties, failure to thrive, the hypotonia, and susceptibility to infection characteristic of the early stage of this syndrome are taken into account, one wonders what the true incidence of this condition might have been. How many biochemical diagnoses are made among infants not brought to the attention of consultant pediatricians? How many such infants fail to survive the early months of life? How many may survive a difficult infancy, without having had biochemical tests performed, and appear later with the triad of supravalvular aortic stenosis, mental retardation, and facies – with renal impairment often also present? (see also, discussion of generalized arterial sclerosis of infancy, as resembling the acute hypervitaminosis D syndrome elicited in the laboratory, *vide infra*).

Despite the high frequency of infantile hypercalcemia seen in Great Britain at a time when the vitamin D intake was very high, this was not, even then, a common disease. Although it was estimated in 1955, that at least 55% of British infants were consuming excessive quantities of vitamin D[79] (FIGURE 10) only 5% of admissions of infants six to 12 months of age to the Dundee Royal Infirmary the following year were due to hypercalcemia of infancy.[49] The attention of British physicians was called to the correlation of this syndrome with excessive vitamin D in milk and cereal, as well as in cod liver oil, as early as 1954,[80-83] the year after manufacturers were instructed to increase the fortification of National Dried Milk from 280 I.U. to 500 I.U. of vitamin D to assure delivery when marketed of the full recommended minimum of 280 I.U./dry ounce (allowing for a maximum deterioration of 44%).[83] One physician (Ball)[82] wrote a letter to the editor of Lancet cautioning that as little as 1,000 units per day might give rise to subjective symptoms of hypervitaminosis D, and a physician (Woodcock)[81] on the staff of one of the milk companies, in another letter to the editor, protested the amount of vitamin D that had to be added to milk. He referred to the early work by Jeans,[84] that demonstrated that at a daily intake of 1,800-2,000 units, growth of infants was retarded as compared with that of infants on 340-500 units in cod liver oil or even 135 units of vitamin D in milk. Creery and Neill[80] of Belfast concurred, the same year, that providing optimum or higher vitamin D intakes from both milk and cod liver oil might be related to the syndrome of hypercalcemia in infants with hypersusceptibility to the vitamin. The British Pediatric Association issued a report dated July 1955,[73, 83] in which they referred to their 1943 recommendation of daily intake (in cod liver oil) of 500-700 I.U. of vitamin D.[85] In view of the high incidence of hypercalcemia and the high vitamin D

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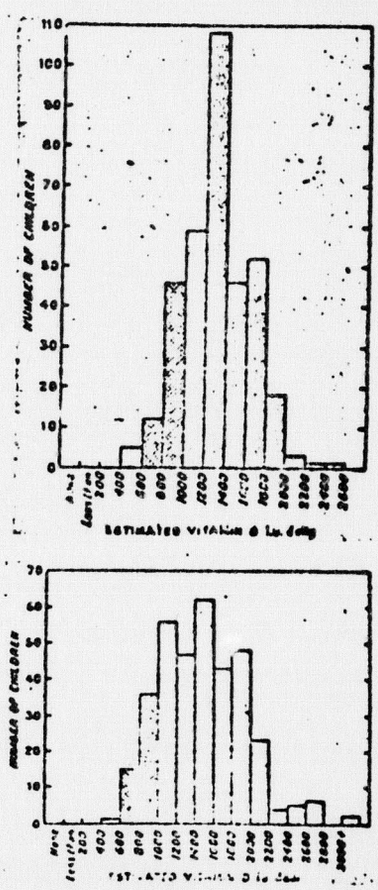


FIGURE 10. (top) Of 351 babies fed on national dried milk, 249 (70.9%) had vitamin D supplements: 208 had cod-liver-oil compound; 30 had adexolin; four had halibut-liver oil; and seven had other preparations. (bottom) Of 348 babies fed on proprietary brands of dried milk, 263 (75.6%) had vitamin D supplements: 172 had cod-liver-oil compound; 65 had adexolin; 16 had halibut-liver oil; and ten had other preparations. (Reproduced by permission of Creery, R.D.G. & D.W. Neill and Lancet.)

content of Welfare and proprietary infant foods (see TABLES 1A and 1B), they recommended that infant requirements of vitamin D be reconsidered, and that the amount added to food be lowered. An editorial, in 1956, speculated whether a hypercalcemic infant who was hypersensitive to calciferol (added to dried milk, cereals, and many concentrates) would be similarly affected by the natural vitamin D found in fish-liver oils.[86] Hubble,[87] in 1956, raised the question whether addition of vitamin D to milk and cereals might cause maximal absorption of calcium and phosphorus (a point which is discussed later in this paper). In 1957, the Ministry of Health published a report[88] on Welfare food supplementation, in which they recommended reducing (1) the vitamin D content of National Dried Milk to a minimum of 90-100 I.U./dry ounce from the minimum of 280 I.U./dry ounce; (2) the vitamin D content of infant cereals from 1,000 I.U. to 300 I.U./dry ounce; and (3) the vitamin D content of cod liver oil from 800 to 400 I.U./teaspoonful. The solution, thus, was to reduce the content of vitamin D in each of the foods to a level that would protect against rickets, should only one source be consumed. Of necessity, this means that an infant taking all three will be consuming at least three times the anti-rachitic dose. In view of the individual variation in sensitivity to vitamin D, and the demonstrated increase in potency of vitamin D when it is given in milk, (*vide infra*) it is dubious whether this provides a sufficient safety factor against causing infantile hypercalcemia in susceptible children.

In North America, for example, where the Council on Foods and Nutrition of the American Medical Association, since 1941,[89] has considered only milk containing 400 U.S.P. units of vitamin D acceptable, there have been many published reports on infants with hypercalcemia.[25-27,43,44,46,47,51,54,55,61,62,90-103] It must be noted, however, that despite the official recommendation that 400 units of vitamin D from all sources meet the full daily requirement, the common fortification of foods (in addition to vitamin supplements) may lead to daily intakes that may reach as much as 2,000 units/day, or more.[104] Whether the occurrence of hypercalcemia of infancy in Continental Europe and Israel[28-30,48,50,53,59,105-112,121] may also be

**TABLE 1A**

FORTIFICATION OF NATIONAL DRIED MILK

| Date | I.U. Vitamin D per Dry Ounce | Recommendation by |
|---|---|---|
| 1945 | 280 | Ministry of Health[88] |
| 1953 | 500 | Ministry of Food[89] |
| 1957 | 90-100 | Ministry of Health[88] |

**TABLE 1B**

CALCULATED DAILY INTAKE OF VITAMIN D (1956)[89]

| | |
|---|---|
| 1½ pints dried milk (460 U/dry oz.): | 1,725 I.U. |
| 1 ounce cereal (1,000-1,500/dry oz.): | 1,000 – 1,500 I.U. |
| 1 tsp. cod liver oil | 700-800 I.U. |
| Total: | 3,525 – 4,025 I.U. |



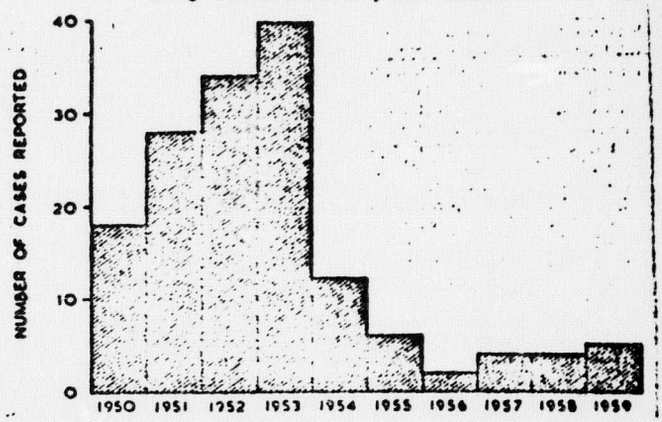


FIGURE 11. Infantile renal tubular acidosis: 153 cases by year of occurrence (14 centers). Information is lacking for 1950 for Liverpool. (Reproduced by permission of Lightwood, R & N. Butler and Brit. Med. J.)

correlated with such moderately high intakes of vitamin D by susceptible infants cannot be averred from available data. It must be noted, however, that in their recent reports of 55 cases of supravalvular aortic stenosis, 23 of whom had clear manifestations of hypercalcemia, Beuren *et al.*[28-30] did attribute the high incidence of these disorders in Germany to high intakes of vitamin D during infancy, and to high susceptibility to vitamin D of affected children.

### *Renal Acidosis and Vitamin D*

Another disease of infancy that has been correlated with vitamin D intake and that is possibly related to hypercalcemia of infancy is renal acidosis. Lightwood and Butler[113] observed that there was a steady increase in the incidence of this disease from 1950 (the first date in the reported tabulation) through 1953, at which time there was a sharp drop in incidence (see FIGURE 11). Since infants with this syndrome often exhibit elevated serum calcium levels, it was reasoned that there was clearly a biochemical overlap between infantile hypercalcemia and infantile renal tubular acidoses. It was concluded, however, that vitamin D was probably not the common etiological denominator, since the drop in incidence occurred in 1954, three years preceding the correction of the excess vitamin D milk content. One point that was not considered, however, was that, from 1945 to 1953, the calciferol content of milk was still excessive (280 I.U./dry ounce), cod liver oil enriched with extra vitamin D was commonly administered in addition, and during that period of time supplementation of infant cereals with vitamin D was also coming into vogue. The drop in incidence of infantile renal acidosis in 1954 coincided with the sharp rise in incidence of hypercalcemia of infancy. The biochemical overlap

between the two conditions suggests that those infants who developed the full-blown syndrome of hypercalcemia of infancy, which includes renal impairment and renal calcinosis, may well have developed renal tubular acidosis on half the amount of vitamin D. The symptoms common to infantile renal acidosis include failure to thrive, vomiting, and growth retardation, symptoms that are characteristic also of hypercalcemia of infancy.[38,67,114,115]

The association of renal acidosis with infantile hypercalcemia has been pointed out by Graham,[49] who published a summary report on 38 infants with hypercalcemia, seen at the hospital of the University of Glasgow, and on nine additional cases of hypercalcemia complicating renal acidosis during the same period. Except for the low carbon dioxide content of the plasma, the findings of all 47 infants were essentially the same. Renal calcinosis is common to both diseases. The author commented that in this hospital, renal acidosis uncomplicated by hypercalcemia was rarely seen. In a study of 60 cases of nephrocalcinosis infantum, detected at autopsy, Shanks and MacDonald[116] observed that only 12 had belonged to the "renal acidosis" group: four were diagnosed as hyperchloremic renal acidosis, seven as idiopathic hypercalcemia, and one child had both. It was apparent that only a few of the children were recognized in life to have been suffering from one of the known causes of nephrocalcinosis. On going back over the records, vomiting was found to have been reported in 40, and constipation in 21. Prolonged administration of fortified milk and/or vitamin supplements were reported in the histories of 52. The authors presented the theory that symptomless hypercalcemia is a more widespread condition than has been appreciated, and that the resultant renal lesions may be detected only when the child happens to die of some other condition. It is noteworthy that in the Table giving the ante-mortem diagnoses of these patients (see TABLE 2), congenital cardiovascular abnormalities were listed in six instances, congenital central nervous system abnormalities in ten, and other renal abnormalities in three.

**TABLE 2**

DIAGNOSES OF 60 CASES OF NEPHROCALCINOSIS SEEN DURING 1948-57

| | Congenital Abnormality | Infection | Miscellaneous | Total | Percentage Total Cases |
|---|---|---|---|---|---|
| System | | | | | |
| Alimentary | | | | | |
| Respiratory | 5 | 14 | | | |
| Cardiovascular | – | 16 | 8 | 27 | 45 |
| Central nervous | 6 | – | – | 16 | 26 |
| Genito-urinary | 10 | 4 | – | 6 | 10 |
| Renal tubular | | | 4 | 18 | 30 |
| Skeletal | | | | | |
| Miscellaneous | 1 | 1 | | | |
| Combined | | | 1 | 3 | 5 |
| Renal calculus | | | | | |
| Renal stones | | | | | |
| Renal hypertension | | | 5 | | |
| Others | | | 8 | | |
| | | | 1 | | |
| | | | 6 | | |

From GRAHAM & A.M. MACDONALD. 1959. Arch. Dis. Child. 34: 115–119.



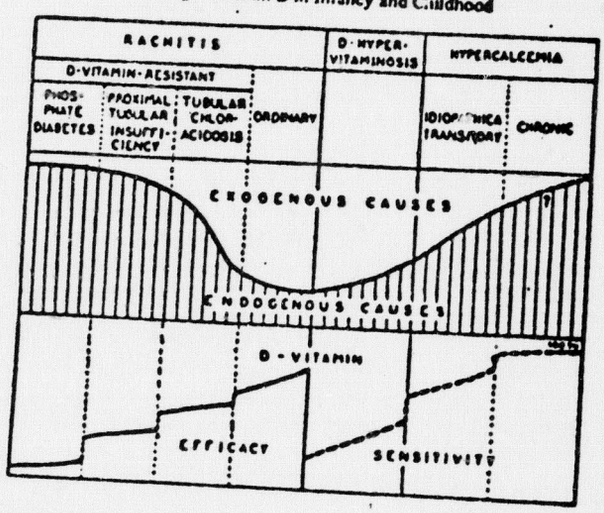


FIGURE 12. Spectrum of varying reactions to vitamin D. (Reproduced by permission of Fanconi, G. and Little, Brown & Co.)

## DIFFERENCES IN SUSCEPTIBILITY TO VITAMIN D

Susceptibility to vitamin D ranges from that of children who require very large doses to prevent rickets to that of infants who respond to doses of vitamin D that are normally prophylactic by developing hypercalcemia. The diagram (FIGURE 12) from Fanconi[117] depicts the spectrum of response to vitamin D. In referring to vitamin D-resistant renal rickets, it is important to note that vitamin D is contra-indicated in the hyperphosphatemic form, and in that associated with renal hyperchloremic acidosis. In the progressive form, in which the serum phosphate may be normal or low, nephrocalcinosis develops. As has been mentioned, the similarity of the findings in infantile hypercalcemia to those of hypervitaminosis D, in the face of intakes that were not excessive, has led to consideration of the possibility that the afflicted children are hyperreactive to vitamin D.[1,22,23,36,38,47-63,65,67,77,86,90-92,95-99,101,103,105,117-119,121]

Positive proof of vitamin intakes at periods of life earlier than that at which diagnosis is made is difficult to obtain retrospectively. Only a few infants, diagnosed as hypercalcemic during the first four months of life, had their intakes of vitamin D reported by the investigators. The infant reported by Stapleton *et al*,[66] who was diagnosed at four months of age with the early characteristics of vomiting, constipation, cessation of weight gain, azotemia, systolic murmur, and hypertension, had had no vitamin D for the first half month other than that in National Dried Milk which was used to supplement breast feeding. From then

on, the total daily intake of vitamin D from the milk formula was about 600 units. Once hypercalcemia was detected at four months, he was put on a low-calcium formula that also lacked vitamin D. The systolic murmur disappeared in one month; at 11 months he seemed normal. It was noted that the mother of this infant had received no pre-natal vitamin supplementation. The three infants reported by Michael *et al*[97] similarly recovered on discontinuing vitamin D and being put on a low calcium diet. In one instance, the infant had received only 130 units daily for the first month, and 640 units of vitamin D daily for ten days until the diagnosis was made at [illegible] weeks. Another infant received a total of 375 units daily for the first month, and 1,000 units a day for the next three months, and then 2,000 units a day for one week until the diagnosis was made. The third infant in this series received a total daily dosage of 650 units for two months before diagnosis. The infant reported by Wilkerson,[96] who died at 15 weeks of age, had never received more than 500 units daily. The condition of this infant, who had marked arterio-venous, renal, and soft tissue calcinosis, as well as hypercalcemia, may well be classified as generalized arteriosclerosis of infancy, which is compared later in this paper to the acute form of experimental hypervitaminosis D.

Among the infants diagnosed as hypercalcemic at six to 20 months of age, the early vitamin D intakes were estimated at having been probably not over 2,000 units daily in over 50 cases. One of the patients reported early by Lowe *et al.*[66] who was diagnosed at eleven months, but whose onset of clinically manifest disease was estimated from the history to have been at five months, had been breast-fed to three weeks of age, and had then been on cow's milk (probably not fortified). The intake of vitamin D from other supplemented foods was not taken into consideration. Another infant in this series had been breast-fed for four months, and was then given National Dried Milk formula until seven months, at which time clinical signs developed that led to the diagnosis of hypercalcemia at ten months of age. The third infant, who had been breast-fed for 11 weeks before being put on National Dried Milk formula, showed the first signs of the hypercalcemic syndrome at four and a half months, and was diagnosed at seven months. The remaining three infants in this series of cases had been on the fortified milk from birth. Only one of these six infants was also given cod liver oil supplements. Five survived and showed some clinical improvement on hospital diets lacking vitamin D. In this group, it is probable that after three to four months of age, all but one had received somewhat over 1,400 units of vitamin D, when all sources are considered. Total daily vitamin D intakes ranging from 500–1,400 units were reported for five infants by Forfar *et al.*,[67] who three years later reported[77] that among 20 hypercalcemic infants (possibly including the five children reported previously), only rarely had any received more vitamin D than that considered optimal. Schlesinger *et al.*[23] reported that among the ten hypercalcemic infants seen by them, they were unable to find any evidence of abnormally high intakes of vitamin D by the infants, or by their mothers, prenatally, in the four cases they were able to investigate fully. However, four of the infants had received National Dried Milk formula and vitamin supplements and thus may have received as much as 2,000 units daily, from all sources. One, who had had a history of milk intolerance, was described as having received only 750 units in cod liver oil. In this instance, it is possible that the "milk intolerance" may have been an early manifestation of vitamin D toxicity from the National Dried Milk formula. One of the infants had been breast-fed and received "vitamin supplements" until six months of age. In this instance, the diagnosis was made at 14 months. Among the 38 infants



with hypercalcemia reported by Graham,[49] ten had received under 1,000 units daily, and two had no history of vitamin D supplementation. The infant reported by Bonham-Carter *et al.*,[43] whose condition was diagnosed as hypercalcemia at nine months, had been breast-fed for three months before being placed on a fortified milk formula. There was no history elicited of excessive fortification, although this infant developed his syndrome during the period of excessive addition of vitamin D to infant foods and dried milk in England. Other infants reported from Great Britain during that time as not having received undue amounts of vitamin D include those reported by Stapleton *et al.*,[56] who, from their experience, postulated that there may be some humans who need no exogenous vitamin D, whereas others need much more than normal amounts.

Infantile hypercalcemia in American infants who had received total daily intakes of 1,200–1,400 units were reported by Bongiovanni *et al.*[98] in two cases, and by Schwartz,[42] Snyder,[45] Garcia *et al.*,[35] and Rashkind *et al.*[96] in a total of four more. Histories of somewhat lower vitamin D intakes were reported by Fellers and Schwartz[91] in three infants, who were shown to have very high blood levels of vitamin D (20–30 times normal values). David *et al.*'s[93] patient had no record of excessive vitamin D, although the exact intake had not been elicited. Daeschner and Daeschner's[92] patient, who died at 32 months, had had a daily vitamin intake of 1,000 units. The three hypercalcemic infants diagnosed at eight months by Fraser *et al.*[26] in Canada, had received no more than 800–1,000 units of vitamin D daily. In two instances, the mothers were known to have received 1,000 units daily of vitamin D during pregnancy.

Histories of supplementation early in infancy, although not very reliable when obtained from families of children diagnosed in later childhood, seem to indicate that in at least 11 instances, excessively high intakes were unlikely. Black and Bonham-Carter[7] obtained data that indicated that among their five cases diagnosed in late childhood, two had had "usual" supplementation, and three had been breast-fed for one and a half to six months, before receiving "usual" care. In two of the instances, the mothers reported that they had received the "usual" vitamin supplements prenatally. Seven such patients reported in the United States had histories of irregular vitamin supplementation,[54] no more than "usual prophylactic doses,"[93,102] 1,000–1,500 units daily for five years,[58] and less than 1,000 units daily.[103] The last two patients, twins reported by Wiltse *et al.*[103] were born to a mother who had received less than 1,000 units of vitamin D/day during pregnancy. The patient reported by Gribetz and Wolf[102] is of interest in that hypercalcemia, renal damage, abnormal electrocardiographic tracings and apical systolic murmur and osteosclerosis were diagnosed at ten years of age. His history suggested possible mild hypercalcemia during infancy, at which time he had had polyuria, polydypsia, and retarded growth, but no apparent mental retardation. Exploration parathyroid surgery at the age of 11 revealed normal parathyroids; follow-up three years later revealed a bright child, who had undergone a marked adolescent growth spurt. In retrospect, the investigators concluded that the history of this boy, and his blood laboratory findings, which included not only hypercalcemia, but also slightly elevated serum cholesterol, phospholipids and lipoproteins, suggested an intermediate form of idiopathic hypercalcemia.

In one of the early studies, Bonham-Carter *et al.*[43] found that loading of a hypercalcemic baby in remission with high doses of calciferol led to deterioration of his condition, concomitant with a rise in plasma calcium. On verification of the role of vitamin D, his intake of vitamin D and calcium was reduced with

subsequent improvement. Hubble,[87] however, gave large doses of vitamin D to two children with the mild form of the syndrome, without producing recurrence of untoward symptoms. Forfar[120] has administered large doses of calciferol (50,000–100,000 units) for about a week to three infants with hypercalcemia. In two instances, after a few days, the serum calcium rose significantly. It took about three weeks for the serum calcium to fall to pre-calciferol levels. In one case the serum calcium level fell, following the administration of calciferol, and rose again to the pre-calciferol level within a day of stopping treatment. Although hypercalcemia is an essential feature of the syndrome under discussion, the response to vitamin D loads and the degree of elevation of serum calcium apparently differ from case to case. Fraser *et al.*[26] have recently commented on the wide fluctuations in serum calcium which they have observed to occur spontaneously during the acute phase of the disease. Using reproducible methods for measuring serum calcium, they have seen variations of 2 to 3 mg per 100 ml within a few days in a single hypercalcemic patient. Girardet[117] has suggested that in certain individuals, even large doses of vitamin D may produce toxic effects without causing a substantial or sustained rise in serum calcium. His impression was based on the development of transitory albuminuria and cylindruria, with elevated NPN, after administration of single doses of vitamin D as large as 600,000 units, despite rapid return to normal of blood calcium levels that did not exceed 11 mg%.

Metabolic balance studies, showing the high percentage of dietary calcium that is absorbed (60%), has suggested to investigators that either an overaction of vitamin D,[43,52] or defective inactivation of vitamin D[47] might cause the syndrome. Assays of vitamin D in the plasma of hypercalcemic infants have led to determination of insignificant differences from normal values in two reports,[119,121] and to clear demonstration of markedly higher than normal values in others.[25,58,90,91] Black[38] has tabulated the serum levels of vitamin D in published reports of different degrees of infantile hypercalcemia and has commented on the conflicting results. He called attention to the failure of the currently used rat line test to demonstrate the vitamin D equivalence (in man) of dihydrotachysterol (Thomas *et al.*[100]). He has cautioned that it should not be assumed that the rat test for vitamin D activity necessarily will detect every agent in the serum which is capable of raising the serum calcium level in the human infant.

Garcia *et al.*[28] reported a serum value of 1,540 units in a child whose supravalvular aortic stenosis was correlated with hypercalcemia, and whose daily vitamin D intake was 400 units from milk and 1,000 units from a supplement. (The normal range of serum vitamin D in this institution was 60–400 units.) Fellers and Schwartz,[90,91] reported serum vitamin D activity of three patients with hypercalcemia to be 20 to 30 times that seen in normal infants, even in the absence of exogenous vitamin D. Two of a set of triplets, whose vitamin D intake during their first half year of life far exceeded the amounts now considered advisable, were diagnosed by Manios *et al.*[122] as hypercalcemic by their 23rd month, at which time all vitamin D was removed from their diets. Manios and Antener[105] then, three months later, demonstrated that serum vitamin D levels rose twofold from pretreatment values of 520 and 580 (as compared with the normal mean of 133 units, and the average range of 50 to 200 units), following administration of 700 I.U./d vitamin D in oil for four days.

These observations suggest that a defect in the metabolism of this vitamin plays a role in this condition. Forfar and his co-workers[67,77,120] observed a marked increase in the free cholesterol, as well as in the calcium levels in

E680



hypercalcemic infants. In view of the vitamin D-like effect of some cholesterol derivatives, these investigators have suggested that this disease may be related primarily to a disorder of cholesterol metabolism. In his doctoral thesis,[120] Forfar has postulated that calciferol may act as a chemical mediator in this disease by activating endogenous vitamin D precursors present in excess in susceptible infants. This concept may explain the relatively small intake of vitamin D associated with hypercalcemia of infancy, and the prolonged vitamin D activity in such infants after withdrawal of all exogenous sources. Black[38] has reviewed several theories involving vitamin D indirectly in the pathogenesis of infantile hypercalcemia. These include (1) deficiency of unsaturated fatty acids, (2) adrenal insufficiency, and (3) hypothyroidism, as well as the disordered cholesterol metabolism already referred to.

### *Reactivity to Vitamin D by Race*

Variations in endogenous precursors may explain the marked variations in susceptibility to rickets seen in different racial groups. In a study in Toronto, reported in 1937 by Drake,[123] of 244 infants of British or Northern European stock, who had received no vitamin D, only 13% had rickets of a moderate or marked degree. At the end of a five-month observation period, 21% had active advancing rickets. The preceding year, Lewis[124] included a control group of 22 infants on no vitamin D in a New York City study of vitamin requirements. Of these infants, observed during a five-month period from December through April, eight or 36.3%, developed rickets. None of the white children in this control group was affected, whereas eight of the 13 Negro children developed roentgenographic evidence of rickets. Thus, of the Negro infants, rickets developed in 62% of those receiving no vitamin D. Of the 27 infants who received crystalline vitamin D in various doses and who developed rickets, 21, or 78%, were Negro. (In this study 55% of the infants were Negro, and 45% Puerto Rican or Italian.) Follis *et al.*[125,126] reported that in a series of 1,303 subjects coming to autopsy during the first two years of life, about 50% of the infants who had definite histories of receiving no vitamin D had rickets. In this group, also, it was observed that the rachitic lesions were more prevalent and severe in Negro children than in whites.

The amount of vitamin D required by the two racial groups to heal rickets or to prevent rickets was also found to vary markedly. In Drake's study,[123] as little as 300 USP units of vitamin D, administered as irradiated ergosterol, were sufficient to heal rapidly rickets of moderate or marked degree. As little as 95 units daily in irradiated milk, or 150 units of vitamin D as cod liver oil or viosterol supplements, prevented the development of rickets. No evidence was obtained that this small amount was less effective in preventing rickets, as measured by roentgenograms, than were the larger amounts usually administered. In the population group reported by Lewis,[124] larger amounts of vitamin D were required to prevent rickets. His data showed that about 14% of 58 infants given 145 USP units in oil or propylene glycol developed moderate to severe rickets, but only 5% showed mild rachitic changes if given the same dose of vitamin D in milk. When the dose of vitamin D in oil or propylene glycol was increased to 290 units, 10% of 51 infants developed rickets; 2% showed early changes on 290 units in milk. On increasing the dose of crystalline vitamin D in corn oil to 1,450 USP units, one Negro child developed a mild form of the disease. Since no hazard was envisioned from such a dose, he recommended addition of 332 USP units to milk to achieve at least this potency. A later paper

by Glaser *et al.*[127] presented evidence that all preparations of vitamin D in an oily vehicle, given as vitamin $D_2$ (prepared by electron activation of ergosterol), viosterol (ultraviolet-irradiated ergosterol), crystalline $D_2$, or vitamin $D_3$ (ultraviolet-irradiated 7-dehydrotachysterol), were effective in daily doses of 100 units in preventing clinical rickets even in premature and in Negro infants. However, because nine infants developed roentgenographic evidence, or suspicion of rickets, among the 166 who were followed for the full observation period of eight months, the authors recommended the use of 400–800 units (in oil) as a prophylactic dose.

Some insight into the difference in vitamin D requirements by racial groups may be gained by examining the findings of Warkany and Mabon.[128] They tested blood samples from 34 white children and 26 Negro children (see TABLE 3) and found that the average value of 122.6 units for the white children was about 15% higher than that for the Negro children (106.5 units). Perhaps more significant in considering factors that may play a role in diseases that may be caused by either a hypersusceptibility or a hyposusceptibility to vitamin D is the distribution of values. Six of the white children had levels twice as high as those of nine of the black children (165 and 83 units, respectively). The possibility that the generally higher anti-rachitic blood levels and greater response to vitamin D in white than in Negro children may be a consequence of the screening of ultra-violet rays by the skin pigment must be considered.

TABLE 3

FREQUENCY DISTRIBUTION OF PERSONS ACCORDING TO LEVELS OF VITAMIN D IN BLOOD SERUM

| U.S.P. Units per 100 cc. of Blood Serum | Total No. Tested | White Adults | White Children | Negro Children |
|---|---|---|---|---|
| 165 | 9 | 2 | 6 | 1 |
| 132 | 27 | 10 | 11 | 6 |
| 110 | 31 | 14 | 10 | 7 |
| 94 | 8 | 2 | 4 | 2 |
| 83 | 13 | 1 | 3 | 9 |
| 66 | 1 | 1 | 0 | 0 |
| Total | 89 | 30 | 34 | 25 |
| Average vitamin D level, units per 100 cc | 116.4 | 117.6 | 122.6 | 106.5 |

From J. Warkany & H.E. Mabon. 1940. American J. Dis. Children.

The work demonstrating the ability of melanin or keratin in the skin to screen out ultra-violet light, thereby allowing for much greater exposure to sun without formation of excessive vitamin D, has recently been summarized by Loomis.[129] On the basis of the observation by Bekenecier[130] that 1 sq cm of white human skin synthesizes up to 18 units of vitamin D in three hours, Loomis[129] calculated that exposure to the skin of the cheeks of fair, thin-skinned children provides about 400 units daily. He postulated that as man moved north, and as he was exposed less and less to the rays of the sun, the fairer-skinned individuals had a survival advantage over those with darker skins,



who were more subject to developing rickets.

It is noteworthy that with only one exception, all of the children with infantile hypercalcemia reported in the literature reviewed in this paper were white. Similarly, generalized infantile arteriosclerosis, a disease not often correlated in the literature with vitamin D, presents a pathological picture that strongly resembles that seen in experimental vitamin D toxicity (*vide infra*), and is also found predominantly in white infants,[131] only two colored infants having been reported with this condition.[98,132] Daeschner *et al.*[114] reported that in a clinic with a significant proportion of Negro or Latin American children, there was a much higher incidence of urinary tract calculi in the white children. Conversely, since the lowering of vitamin D in infant foods and supplements in Great Britain, the incidence of rickets was not found to have increased in white children, but did in colored immigrants.[133]* As for the postulated late normocalcemic stage of infantile hypercalcemia, the Williams' syndrome, that too has been reported predominantly in white children. Several colored children with supravalvular stenosis, however, have been reported.[10,93]

Although the trait responsible for hyper-reactivity to vitamin D predominates in fair-skinned children, it is apparently not limited to that racial group. It seems unlikely that difference in skin pigment, alone, can account for the extremes in reactivity to vitamin D. Additional metabolic differences in handling vitamin D must also exist.

## EFFECT OF VEHICLE ON VITAMIN D POTENCY

The greater efficacy of vitamin D in milk, in preventing rickets, as compared with vitamin D in oil or in propylene glycol,[123,124] was foreshadowed in 1935 by Stearns and Jeans[94,134,135] who calibrated the effect of different doses of vitamin D against the growth of infants. They showed that infants given 300–400 units of vitamin D in cod liver oil grew at faster than average rates, whereas infants getting all of their vitamin D from cod liver oil emulsified in milk required only 135 units per quart for the same rate of growth. Their demonstration that daily vitamin D intakes of 1,800–4,000 units caused a gradual slowing of growth, which immediately increased after the intake had been reduced to 400 units in cod liver oil, has since been criticized as not standing up to modern tests of significance.[36]

The clinical reports by Drake,[122] Lewis,[124] and Stearns and Jeans[94,135] indicated an approximately threefold increase in potency of vitamin D when it was given in milk. An even greater enhancement effect by milk of the potency of vitamin D was indicated by Lewis'[136] clinical experience with the anti-rachitic effect of crystalline ergosterol in oil or in milk (see TABLE 4). He demonstrated that the therapeutic effect of 90 units of crystalline vitamin D in milk healed all nine rachitic infants in his study, as demonstrated by roentgenogram at four, six, eight, and ten weeks. Only 45 units in milk were curative in six out of eight rachitic infants. Of the nine infants who received 90 units in oil, three showed no healing at six weeks, and the rachitic process became worse at the end of eight weeks in two. One of the infants in this group, who showed advancement of the rachitic process at four weeks, was then given 90 units in milk with resultant definite healing in four weeks, and calcification in the rachitic zone

*A few cases of florid rickets have since been reported among white children, in cases of neglect (Editorial, Brit. Med. J. 1966. 558).

TABLE 4

COMPARISON OF HEALING, AMONG 36 RACHITIC INFANTS, BROUGHT ABOUT BY CRYSTALLINE VITAMIN D INCORPORATED IN MILK OR IN CORN OIL

| Case | Age (Mo.) | Date Begun | Menstruum in which Crystalline Vitamin D was Incorporated | No. of Rat Units (Steenbock) Given | Roentgenologic Rickets | | | | | Comment |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | At Onset | Healing after 4 Wk. | Healing after 6 Wk. | Healing after 8 Wk. | Healing after 10 Wk. | |
| C.M. | 8 | 1/23 | Milk† | 45 | Moderate | + | ++ | +++ | ++++ | Porto Rican |
| B.G. | 6 | 1/25 | | | Moderate | + | +± | ++ | ++± | Porto Rican |
| F.S. | 13 | 1/26 | | | Moderate | 0 | 0 | | | Negro |
| E.D. | 6 | 2/7 | | | Slight | + | ++ | +++± | | Italian |
| G.N. | 8 | 2/18 | | | Moderate | + | +± | ++ | +++ | Porto Rican |
| C.W. | 22 | 2/17 | | | Marked | +± | ++ | ++± | | Negro |
| G.B. | 8 | 2/21 | | | Moderate | +± | ++± | +++± | | Negro |
| J.N. | 6 | 2/24 | | | Mild | 0 | 0 | 0 (worse) | | Negro |
| V.L. | 6 | 1/13 | Milk‡ | 90 | Slight | ++ | +++ | Normal | ++++ | Italian |
| S.Q. | 4 | 1/13 | | | Moderate | +± | ++± | +++± | | Porto Rican |
| J.A. | 5 | 1/13 | | | Slight | +++ | ++++ | Normal | | Negro |
| R.L. | 5 | 1/19 | | | Moderate | +++ | Normal | Normal | Normal | Negro |
| C.H. | 20 | 1/25 | | | Marked | +++ | +++± | ++++ | Normal | Negro—1/25: calcium, 9.8 mg.; phosphorus, 3 mg. 2/23: calcium, 10.6 mg.; phosphorus, 5 mg. |
| K.S. | 4 | 2/22 | | | | | | | | Negro |
| B.C. | 7 | 3/2 | | | Slight | ++ | +++ | Normal | | Porto Rican |
| F.S. | 15 | 3/17 | | | Moderate | + | | | | Negro |
| B.R. | 6 | 3/17 | | | Moderate | + | +± | | | This infant had received 90 units of crystalline vitamin D in oil for one month, and no healing resulted |
| | | | | | Moderate | +± | +++ | | | |

TABLE 4 (cont)

| Case | Age (Mo.) | Date Begun | Menstruum in which Crystalline Vitamin D was Incorporated | No. of Rat Units (Steenbock) Given | Roentgenologic Rickets | | | | | Comment |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | At Onset | Healing After 4 Wk. | Healing After 6 Wk. | Healing After 8 Wk. | Healing After 10 Wk. | |
| T.R. | 5 | 2/4 | Oil‡ | 90 | Moderate | +± | ++± | +++ | ++++ | Porto Rican |
| S.L. | 7 | 2/12 | | | Slight | ? | + | +± | | |
| B.M. | 4 | 2/14 | | | Slight | + | ++ | | ++ | Negro |
| B.R. | 5 | 2/16 | | | Slight | 0 (worse) | | | | Negro |
| V.B. | 14 | 2/16 | | | Marked | + | +± | ++ | +++ | Negro |
| D.R. | 7 | 2/21 | | | Moderate | 0 | 0 | 0 (worse) | 0 | Negro |
| C.Q. | 5 | 2/23 | | | Slight | ? | + | +± | ++± | Porto Rican |
| C.B. | 8 | 2/28 | | | Moderate | 0 | 0 | 0 (worse) | | Negro |
| T.B. | 8 | 3/19 | | | Moderate | 0 | 0 | | | Negro |
| J.B. | 3 | 2/15 | Oil§ | 900 | Slight | ++ | | Normal | Normal | Negro |
| P.G. | 6 | 2/9 | | | Slight | ++ | ++++ | | | Italian |
| J.B. | 6 | 2/16 | | | Slight | ++ | ++± | +++ | +++± | Negro |
| T.B. | 6 | 2/16 | | | Slight | ++ | ++++ | Normal | | Negro |
| C.M. | 6 | 2/16 | | | Moderate | ++ | | | | Negro |
| R.P. | 17 | 2/17 | | | Marked | + | | | | Negro |
| H.B. | 4 | 2/17 | | | Slight | ++ | +++ | +++± | Normal | Negro |
| J.D. | 7 | 2/17 | | | Moderate | ++ | +++± | +++ | +++± | Negro |
| N.E. | 3 | 2/17 | | | Slight | + | ++ | +++± | | 2/15: calcium, 7.7 mg.; phosphorus, 5.3 mg. 2/19: calcium, 10.3 mg.; phosphorus, 6.1 mg. |
| J.D. | 24 | 1/30 | | | Marked | + | + | + | +± | Negro; at 12 weeks healing ++ |

*X-ray picture taken at 13 weeks.
†One liter contained 60 units.
‡One liter contained 120 units.
§One drop contained 5 units.
§One drop contained 150 units.
+Denotes slight healing; ++, moderate healing; +++, marked healing; ++++, healed rickets.

From LEWIS, J.M. 1935. J. Pediatrics 6:363-375.



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two weeks later. Administration of 900 units of vitamin D in oil to ten rachitic infants resulted in beginning improvement within four weeks in all. One Negro baby, however, who had marked rickets, showed only slight to moderate healing by the end of 12 weeks. Lewis concluded that the 900 units in oil was a good therapeutic dose for mild or moderate cases of rickets, but might not be adequate for severe forms. He commented that the therapeutic results obtained from 90 units in milk were superior to those obtained with 900 units in oil.

Supplee *et al.*,[137] intrigued by the evidence that vitamin D in milk was a more effective anti-rachitic agent than vitamin D in oil, undertook an evaluation of the factors in milk that might have accounted for this enhancement effect. Using the rachitic rat assay technic, they found marked differences in the anti-rachitic response, depending on the vehicle in which the vitamin D had been delivered. Milk and even an isolated milk constituent, lactalbumin, were shown to have enhanced the potency of vitamin D. The combination of the lipid-free lactalbumin with the vitamin was found to have exhibited a greater anti-rachitic potential than the lactalbumin-vitamin in combination with lipids. They concluded that vitamin D administered in the water phase was more effective clinically than when administered in an oil vehicle.

Since vitamin D in milk is much more active than when it is administered in oil, the addition of 400 units to a quart of milk may be the equivalent of several times that quantity administered in oil. For the children with a high intake of milk, it can be presumed that the daily intake of vitamin D is undoubtedly higher. Were there no risk in providing therapeutic dosages of vitamin D to the entire population instead of prophylactic doses, this excess over that considered sufficient by the Committee on Nutrition of the American Pediatric Association (400 units from all sources)[104] could be safely disregarded. There is evidence, however, that infantile hypercalceimia, renal acidosis, and nephrocalcinosis may well be related to moderately high intakes of vitamin D by children with high susceptibility to this vitamin.

## HISTOPATHOLOGIC FINDINGS IN ANIMALS WITH EVIDENCE OF VITAMIN D-TOXICITY: CORRELATION WITH CLINICAL SYNDROMES

It is clear from the foregoing that there is a wide range of response to vitamin D. A dose little more than that usually necessary to prevent rickets may produce severe toxicity in some children even though it is well tolerated by most. The lesions produced in such susceptible children are very similar to those produced in experimental animals by toxic doses of vitamin D.

### *Experimental Hypervitaminosis D*

As early as 1927–1928, Pfannenstiel[138] and Kreitmair and Moll[139] reported pathological changes in animals given large doses of irradiated ergosterol. Kreitmair and Moll[139] described the pathological effects of 0.2 to 10.0 mg/day in mice, rats, guinea pigs, rabbits, cats, and dogs. Death ensued after six days to three months; postmortem changes included massive deposits of calcium in arteries, kidneys, heart, and other organs. In 1929 Harris and Moore[140] showed that the toxic effects are specifically attributable to the vitamin. Duguid[141] observed, in 1930, that there was a considerable variation in susceptibility of their rats to 10 mg of irradiated ergosterol in olive oil fed for a maximum of 34 days. Of 120 rats fed the supplement for 25 days, only 71 showed aortic lesions, and 92 showed lesions in the kidneys. The earliest signs of vitamin D toxicity developed in the kidneys, which showed calcareous casts in the tubules and, occasionally, calcification of the interstitial tissue. One of the aortic lesions found chiefly in the media consisted of muscular degeneration. Calcification of the elastic lamina seemed to have occurred early, with calcification in the muscular element of the media occurring only following the degenerative changes. Such calcification was seen first and most frequently in the ascending portion of the aorta, including the sinus of Valsalva. The intimal changes, which were minimal, were considered to have been secondary to the medial changes. A year later Vanderveer[142] injected young rabbits subcutaneously with 5 cc/kg of irradiated ergosterol twice weekly until the deaths of the animals. He, too, found the earliest calcareous lesions to have been intimately related to the elastic fibers of the aorta. In these experiments, the calcium was deposited over the elastic fibers and muscle cells before either showed degenerative changes. Focal areas of muscle degeneration were seen in the aorta. In some animals, extensive calcium deposition was seen in the myocardium, as was some sclerosis of the coronary arteries. Generally there were calcium casts in the tubules of the renal cortex, and in some animals there were also parenchymal calcareous deposits. Interested in the sequence of development of the deforming, sclerotic changes of the ascending and transverse portions of the aortas of animals that died of poisoning with vitamin D, Spies[143] studied the effect of sublethal dosage on young rabbits. They were sacrificed 97–102 days after the final dose of viosterol was given. The walls of the ascending aorta and transverse arch were calcified, irregular, and tortuous. There was aneurysmal dilatation in some areas and reduction in caliber of the vessels in others (caused by protrusion inward of the arterial lesions). The internal elastic lamina of the media was most severely affected. Comparison of the lesions of this group of animals with those of rabbits given massive doses that caused death[144] led Spies to speculate that degeneration of the affected cells and reabsorption of some of the calcium may have taken place after ceasing vitamin D administration. Similarly, the kidneys of these rabbits had strikingly fewer calcium deposits than those of the acutely poisoned animals, suggesting to the investigator that the calcium deposits may have been reduced.

To determine whether the calcifications caused by vitamin D toxicity were degenerative changes, or merely due to precipitation of calcium from the blood, Ham[145] administered enormous single doses of irradiated ergosterol to one series of rats, and daily doses to another. Twenty-four hours after the single dose, no lesions were seen; within 48 hours massive calcifications were seen in the aorta, coronary arteries, and cardiac musculature, around which was a marked inflammatory cell infiltration. He concluded that, among other factors, the precipitation of the calcium depended on the saturation of the serum with diffusible calcium. On the other hand, Steck *et al.*[146] found evidence, in a study of 64 dogs given 15,000–500,000 units of vitamin D/kg daily, that cellular injury occurs first and that calcium deposition then takes place at the site of injury. The influence of vitamin D on the calcium and phosphorus content of tissues of dogs was studied by Reed *et al.*[147] in 1933. Dogs on high dosage irradiated ergosterol showed higher concentrations of calcium in all tissues analyzed (see TABLE 5). The greatest increments were seen in the heart and kidneys. The increase in the content of calcium in the brain is of particular interest, since it provides a clue to the cerebral damage that is probably associated with the mental retardation seen in children with infantile hypercalceimia. There was no direct correlation between the calcium content of the tissues and the total amount of viosterol injected per kilogram of body weight or

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TABLE 9

THE CALCIFICATION OF TISSUES BY EXCESSIVE DOSES OF IRRADIATED ERGOSTEROL

Calcium, mg per 100 g

| Tissue | Normal mean a | Ergosterolized mean b | $E_\Delta=\sqrt{a^2+b^2}$* | $\Delta/E_\Delta$ † | Probability |
|---|---|---|---|---|---|
| Adrenal | 37.6 ± 3.24 | 203.1± [illegible] | 81.9 | 2.02 | 0.04 |
| Aorta | 64.23± 6.84 | 175.3± 35.7 | 35.9 | >3 | <0.01 |
| Brain | 55.4 ±14 | 125 ± 16.7 | 21.8 | >3 | <0.01 |
| R. ventricle | 2.27± 4.43 | 149.6± 37.69 | 37.9 | 2.9 | <0.01 |
| L. ventricle | 18.3 ± 1.64 | 220.4± 63 | 64 | >3 | <0.01 |
| Kidney | 55.6 ±15.9 | 671.6±236.3 | 236.8 | 2.6 | <0.01 |
| Liver | 17.9 ± 1.22 | 122.8± 45.1 | 45.5 | 2.33 | 0.02 |
| Lung | 88.6 ±13.2 | 338.4±160.2 | 165 | 1.514 | 0.13 |
| Muscle | 17.8 ± 1.16 | 64.8± 13.3 | 13.4 | >3 | <0.01 |
| Skin | 23.6 ± 1.95 | 69.8± 16.1 | 16.2 | 2.85 | <0.01 |
| Spleen | 14.3 ± 2.19 | 100.8± 21.26 | 21.4 | >3 | <0.01 |
| Thyroid | 101.3 ±22.9 | 509.3±144.66 | 147 | 2.77 | <0.01 |

Phosphorus, mg per 100 g

| | | | | | |
|---|---|---|---|---|---|
| Adrenal | 595.8 ±30 | 648 ±109.18 | 113.3 | <1 | 0.64 |
| Aorta | 272.2 ±18.4 | 315.4± 13.1 | 28.07 | <1 | 0.12 |
| Brain | 1317.3 ±31.5 | 1018.3±130 | 164 | 1.82 | 0.07 |
| R. ventricle | 708.1 ±37.7 | 736.9± 42.36 | 50.6 | <1 | 0.61 |
| L. ventricle | 767.3 ±50.3 | 694.5± 49.2 | 70.4 | 1.34 | 0.27 |
| Kidney | [illegible].8 ±74.3 | 994 ±126.5 | 146.7 | 1.21 | 0.23 |
| Liver | 790 ±24 | 681.5±104.1 | 106.8 | 1.02 | 0.30 |
| Lung | 865 ±53.3 | 977.6±163.6 | 172 | <1 | 0.51 |
| Muscle | 699.3 ±43.6 | 536.7± 47.7 | 60.4 | 2.19 | 0.03 |
| Skin | 152.3 ±37.1 | 280 ± 50.5 | 62.5 | 2.05 | 0.04 |
| Spleen | 925.1 ±40.8 | 901.3± 59.4 | 72.12 | <1 | 0.74 |
| Thyroid | 554 ±57 | 712.6±119 | 132 | 1.2 | 0.23 |

*$E_\Delta=\sqrt{a^2+b^2}$, a=standard deviation of normal series.
b=standard deviation of experimental series.
†$\Delta/E_\Delta$ Δ=difference between means of the two series

From Reed, C.I., E.A. Dillman, E.A. Thacker, & R.J. Klein. 1933. J. Nutr. 6: 374.

the size of the individual injections. There were wide variations in the amounts of vitamin D that were toxic, but there was a tendency towards a comparable degree of calcium deposition in most of the tissues of any given animal.

Because the arterial sclerosis produced by vitamin D in the experimental animals seemed to have involved primarily the media, whereas that seen in man was usually correlated with intimal damage associated with hypercholesterolemia, Harrison[146] studied the combined effect of sequentially administered cholesterol and vitamin D in rabbits. In those cases in which the vitamin D was given after challenge with cholesterol, medial sclerosis was produced in aortas that were already the seat of severe cholesterol sclerosis,

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although the two different types of lesions were found in different areas and were not superimposed. Both types of lesions favored the proximal half of the aorta including the arch. It is of interest, in this regard, to recall that children with hypercalcemia of infancy have not only elevated calcium levels but also elevated blood cholesterol.

Gillman and Gilbert[149] investigated factors that might explain the greater incidence of cardiovascular disease among the white population, as compared with that among Africans (who consumed diets low in calcium and cholesterol). Differences in metabolism of calcium and phosphorus were considered factors that might play a role in the variations in susceptibility to arteriosclerosis. Since hyperlipemia may exist even when the diet is low in fat, and the deposition of lipids in tissues is dependent upon complex biochemical processes, they considered the possibility that such injury to the arterial wall as was caused by vitamin D might have predisposed to atheromatous plaque formation. In their intensive studies of 300 rats, ranging in age from three to six months, fed one to five daily doses of 25,000 units of vitamin D as crystallized calciferol in oil, they observed a wide range of reactions. It was apparent that not all rats developed toxic reactions to the same dose of the vitamin. One of the commonest reactions seen was mild damage to the arterial endothelium with migration of monocytoid elements and polymorphs into the superficial part of the media and lifting of the overlying endothelium. Necrosis of the intima was associated with metachromasia and disruption of the elastica. Damage to the endothelium and subendothelial tissues in the aorta was confined to the sinus of Valsalva and the first part of the aortic arch. Mild subendothelial edema was accompanied by a variable degree of metachromasia and accumulation of Schiff-positive material. Depending on the degree of involvement, there was lesser or greater infiltration with white cells. The mildest form of medial injury was edema, with presence of Schiff-positive material and metachromasia, changes which were usually preceded by cellular swelling or even endothelial degeneration at the site. Calcification of the elastic lamina, followed by degeneration of the muscle cells, preceded replacement of the degenerated fibers by large, clear, fluid-filled spaces that widely separated the elastic fibers. At this stage, the inner part of the wall was thrown into folds. Intense subendothelial and medial calcification, in some instances, led to the formation of solid plates, which were often progressively covered by multiple layers of endothelial cells. The calcium plate gradually became reduced and more deeply embedded in the mesh thickened wall of the aorta. Animals sacrificed 150 days after the last dose of vitamin D showed aortas with the original calcified portions replaced by a thick, cartilage-like material with calcified tissues forming irregular bands in the deeper layers of the aortas. By graded administrations of vitamin D, Gillman and Gilbert[149] were able to demonstrate that myocardial injury and calcification were preceded by swelling and intense eosinophilia of the muscle cells. After discontinuation of vitamin D, repair of the degenerated myocardial area took place, with hypertrophy of the neighboring muscle cells and reestablishment of the capillary networks. Valvular lesions, the earliest changes in which were subendothelial edema and intense metachromasia similar to that seen in the aorta, were also common after toxic doses of vitamin D. Calcification of the valves was uncommon.

Recently Coleman,[64,65] who demonstrated electrocardiographic changes in patients with infantile hypercalcemia and considered the changes as probably indicative of left ventricular myocardial damage, administered vitamin D in oil orally to 18 young rabbits (40-420 units $D_2$; 100-770 units $D_3$).[65] Aortic lesions were found in every rabbit given vitamin D, but in none of the controls. The inner half of the media was affected, and in some instances there was

intimal thickening. Where there was distortion or disruption of the elastic fibers, and muscle cells were destroyed, there was calcium deposition. Two of the rabbits died in congestive heart failure; four others had focal myocardial lesions, consisting in three of periarterial muscle necrosis, a cellular reaction, and staining reaction suggesting calcium deposition. Ten of the rabbits given vitamin D had lesions immediately subjacent to the endocardium. Serum calcium levels higher than those of control animals were found in the experimental rabbits for 32-38 weeks after discontinuing administration of vitamin D.

It is worthy to note that in the series of experiments with rats reported by Gillman and Gubert,[149] there was another similarity to the syndrome of infantile hypercalcemia, which includes failure to gain weight, atony, and muscle wasting. Toward the end of the five-day period, during which very high doses of vitamin D were given, there was a precipitous loss of weight, with obvious wasting, and severe frank degeneration of the skeletal muscles.

More recent work has emphasized the role of the mucopolysaccharides in the lesions caused by vitamin D.[150-153] Eisenstein and Groff[150] reported that rats given massive doses of vitamin $D_2$ showed not only elevated serum calcium levels but also increases in seromucoid. The deposition of calcium in the soft tissues (renal tubular casts, in myocardium at the site of inflammation, and in the aorta), took place in a matrix composed at least partially of an unidentified polysaccharide. Gillman and Hathorn[151] found that the initial aortic lesions (in rats) appeared six to 15 days after the first dose of calciferol, and were localized around the medial vascular elastic membranes just deep to the intima. Calcification occurred early and was associated with local accumulation of nonsulphated P.A.S.-positive polysaccharide. If the dose of vitamin D was not very high, the initial mineralization sometimes resolved in the next six to ten days, after which the tissue between the injured elastic membranes became laden with metachromatic mucopolysaccharide. In such instances, regeneration of the original vascular architecture took place. With more severe or prolonged injury, fibrosis and scar formation occurred, preceded by localized accumulation of metachromatic, sulphated mucopolysaccharides. In their later studies of the histochemical and chemical changes associated with the soft tissue calcification following acute intoxication with vitamin D, Gillman *et al.*[152] identified the tissue polysaccharides. They, too, found a rise in serum mucopolysaccharides, which was prolonged for about two-thirds of the entire observation period of 160 days in contrast to the hypercalcemia, which persisted for only ten days. The levels of aortic hexose and hexosamine approximately doubled; these increases were not quantitatively related to the calcium content. The laying down of calcium was, however, closely paralleled by large increases in the phosphorus content of the aortas. The total aortic collagen appeared to have increased toward the end of the experimental period, coinciding with the histological appearance of aortic and coronary sclerosis. This group of investigators found that the serum mucoprotein changes of calciferol-intoxicated rats seemed to be more closely associated with necrosis and the subsequent healing process in the heart, kidney, and other soft tissues than with calcification.[153]

Most recently, on the assumption that the supravalvular aortic stenotic lesion may result from intrauterine damage caused by administration of vitamin D to the pregnant mother,[99] Friedman and Roberts[154] studied the young of pregnant rabbits given 1.5-4.5 million units of vitamin D. Since all rabbits on 2.5-4.5 million units died within 65 days after their first injection, the results of the study pertain only to the rabbits given 1.5 million units. The blood levels of the pregnant rabbits and of their offspring were seven and nine times greater than those of the control rabbits and of their young, indicating that transplacental passage had occurred. All of the mothers showed the classic vitamin D-induced changes in the aortas. Fourteen of the 18 newborn rabbits had normal aortas, but 11 of these 14 showed an exaggeration of the supravalvular plica that was similar to that seen in five of the 23 control neonates. Four of the vitamin D-rabbit neonates, each from a different litter, had abnormal aortas. In each there was a prominent annular protrusion at the superior margin of the sinus of Valsalva, with resultant narrowing of the lumen. The protrusion was caused by medial proliferation; the intima was normal. Offspring of vitamin D-mothers that died at two to 20 days showed lesions of the aortas ranging from early medial degeneration and thickening at seven days, to triangular-shaped protrusions into the lumen of the aorta, caused by localized thickening of the aortic media. The six rabbits sacrificed at three months showed changes in their aortas quite similar to those found in the mothers given the vitamin. It should be noted that these changes were very similar to those reported by Gillman and Gilbert[149] late in their 150-day rat study, and by Coleman[64] in young rabbits given very much smaller doses of vitamin D by mouth. Apparently the late results of acute vitamin D toxicity are similar, whether induced *in utero*, or in the young or adult experimental animal.

Note should be taken here of an inadvertent demonstration that administration of large daily doses of vitamin D early during gestation to a mother of a child with infantile hypercalcemia is not necessarily causative of infantile hypercalcemia. To ascertain whether the mother of a four-year-old patient with the supravalvular aortic stenosis-peculiar, facies-mental retardation syndrome was hypersensitive to vitamin D, Forbes *et al.*[155] gave her 10,000 units daily. To their dismay, after two and one-half weeks, the mother reported that she was pregnant. The vitamin D was immediately discontinued, and the milk intake of the mother was restricted to one pint of nonfortified, skim milk daily for the duration of her pregnancy. A normal child was born at term, who has remained normal throughout 18 months of follow-up.

### *Histopathology of Clinical Conditions Resembling Experimental Hypervitaminosis D*

The histopathology described by Perou in clinical supravalvular aortic stenosis,[8] which included hyalinized fibrous tissue, as well as foci of necrosis and calcification, often associated with degenerated elastica within the thickened media of the aortas, bears a striking resemblance to the late lesions reported in the foregoing section. Infants dying early in the course of hypercalcemia had histological aortic changes bearing a significant resemblance to the earlier experimental lesions caused by vitamin D toxicity. Intimal and subendothelial thickenings with fragmentation, degeneration and calcification of the elastica, as well as medial and myocardial degenerative changes have been reported.[22,23,40,52,62,64,95,96]

At the autopsies of infants with generalized arterial calcification, changes resembling even more closely the acute vitamin D toxicity damage seen in laboratory animals have been observed. Stryker,[132] in 1947, reported four infants who died at two to seven months of age, and whose autopsies revealed calcification of the coronary and other arteries, in relationship to the internal elastic lamina. A fifth infant, stillborn to a 14-year-old girl, had similar arterial lesions, as well as focal calcification in the first portion of the aorta, myocardial necrosis and calcification, and multiple developmental anomalies. Foci of recent

myocardial infarction were found in two of the infants who survived the neonatal period; renal damage ranging from cloudy swelling of the parenchyma to marked calcification of the renal tubules was seen in two. Considering the possibility that hypervitaminosis D may be a causal factor in generalized arterial calcification of infancy, Stryker recorded the available information on vitamin D intake in his series of cases, as well as in the 15 cases he tabulated from the literature. In the case of the infant who died at three months, the family physician had suspected hypervitaminosis D but could elicit no history of unusual vitamin intake by either the mother or by the infant. It is of interest that the sibling of this infant was reported by the physician to have died with a similar clinical picture, but no autopsy had been done. The infant who died at seven months had been breast-fed, and had received two drops of a concentrated cod-liver oil twice daily during the first month. No history regarding vitamin D intake was obtained in the remaining three cases. Among the patients tabulated from the literature was one reported by Lightwood[156] of a child who died at 27 months. She had been found to have hypercalcemia (11 mg%) and albuminuria, and at autopsy showed fibrotic and calcified glomeruli, interstitial fibrosis and degeneration, fibrosis, and calcification of glomeruli and tubules. She had osteoporosis and osteosclerosis and was described as mentally retarded and dwarfed. Having been reported as having received only "physiological" amounts of vitamin D, at a time (1932) when there was no vitamin supplementation of food, this may be the first recorded case of infantile hypercalcemia caused by hyper-reactivity to vitamin D. Her mother had taken no vitamin D supplements during pregnancy. Among the remaining 14 infants, tabulated by Stryker, were two reported by Anderson and Schlesinger,[157] who had had moderate hypercalcemia and renal damage but who were reported to have had hyperparathyroidism; one of these two infants however, had received about four times the usual amount of vitamin D. All others had been given a single dose of 300,000 units. Menten and Fetterman[158] reported an infant who died of generalized arteriosclerosis and myocardial infarction, born to a mother who had taken no vitamin D during pregnancy, but who had taken two capsules of dicalcium phosphate daily. He had received five drops of oleum percomorph daily starting at two weeks. At one month he began to vomit; at 54 days he seemed cranky and upset–both symptoms that are now commonly considered characteristic of infantile hypercalcemia. At autopsy, all of the superficial coronary branches were found to be thickened, sclerotic and calcified, and the aorta was diffusely thickened. Histological examination revealed coarsening of the internal and medial elastica fibers of the coronaries, with calcification, and degeneration of elastic fibers of the media of the aorta, with calcareous thickening. Foci of myocardial infarction and fibrosis were present. Hyalinization of about 2% of the glomeruli was noted, as was calcific degeneration of occasional glomeruli and collecting tubules. The remaining two infants reported by Menten and Fetterman[158] were siblings, who died at six and seven weeks, respectively, and who showed generalized arteriosclerosis, myocardial infarction, and parenchymatous degeneration of the kidneys. The commonest change seen in the aorta was swelling and degeneration of irregularly distributed elastic fibers: there were also atheromatous thickenings, with thinning of the underlying media. The infant reported by Wilkerson[98] as having hypercalcemia of infancy, who had severe calcinosis of arteries, kidneys, and soft tissues on autopsy at 17 weeks, and who had never received more than 500 units daily of vitamin D, may also be grouped with the infants described above. Hunt and Leys,[159] who compared the pathological changes seen in two siblings who died at four weeks

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of age with those seen in infantile hypercalcemia,[39, 40] reported a marked predilection for calcification of the internal elastic lumina in the arteries of his patients and of others reported in the literature. In addition to calcification of the peripheral and pulmonary vessels, the infants also had fibrous intimal proliferation to the extent of obliteration of the lumen in some sites, calcium incrustation of the elastica throughout the aortic media, as well as renal calcification. One of these infants showed clear evidence of myocardial infarction, as did an eight-week-old girl reported by Traisman *et al.*[160] and another infant (one of two more siblings with this syndrome) reported by Moran and Becker.[131] The latter report included a summary of 44 published cases of arterial calcification in infancy. In all but two of these case, calcific material was reported in the coronary arteries, and fibrous intimal proliferation was seen in many other arteries in most of the cases.

Specific attention was called to the renal damage seen in the picture of generalized arteriosclerosis of infancy by Stryker,[133] and by Moran and Becker[131] who reviewed the published cases to date in 1947 and 1959, respectively. Moran and Becker suggested that metastatic arterial calcification may occur secondarily to renal damage. Their series of cases excluded any in which there was clear evidence of primary renal disease, although concomitant renal lesions, ranging from "local glomerulonephritis" or "changes" to calcification of renal arteries and/or tissue, was reported in most of the cases. The authors commented that the arterial lesions were indistinguishable from those seen in arterial calcification secondary to advanced renal disease, or associated with anomalies of the heart or great vessels, or known to be caused by hypervitaminosis D.

## DISCUSSION

Among the diseases seen in infancy and childhood are several that seem to be relatively new, at least as regards frequency of reporting in the literature during the past 20 to 25 years. It is difficult to be certain whether supravalvular aortic stenosis (Williams' syndrome), hypercalcemia of infancy, renal acidosis, and generalized arteriosclerosis of infancy are detected more frequently because of the greater sophistication of the clinician, or whether they have actually increased in incidence during the past quarter of a century. That all are characterized by lesions seen in experimental hypervitaminosis D, and that during the same period vitamin D supplementation has become prevalent in those countries from which most of the cases have been reported, has been demonstrated.

The cardiac changes seen in the clinical conditions described bear a striking resemblance to those seen in rats and rabbits on high doses of vitamin D. About a quarter of the infants who died of generalized arteriosclerosis were found to have had myocardial lesions, described as focal necrosis, infarction, fibrosis, and areas of calcification.[131,132,157-160] Such lesions have also been reported in infants who died of infantile hypercalcemia, but far less frequently. In his review of the cardiac lesions of infantile hypercalcemia reported in the literature, and seen in his own clinic, Coleman[56] listed left ventricular or biventricular myocardial hypertrophy, myocardial fibrosis or calcification, and valvular endocardial lesions including fibrosis and calcification. Suspecting a myocardial lesion in one of the children with the supravalvular aortic stenosis syndrome, Williams *et al.*,[3] found that Denie and Verheugt[5] and Burry[4] had reported fibrous myocarditis and myocardial atrophy in similar patients. They suggested

that myocardial degeneration might be another facet of the syndrome. Perou[5] also found evidence of myocardial fibrosis in one of his cases of supravalvular stenosis. If, indeed, these three conditions represent increasingly severe manifestations of excessive response to vitamin D, it is not surprising that in the form characterized by infantile arteriosclerosis, there is focal myocardial necrosis or infarction and calcification, as has been reported in acute vitamin D toxicity studies in rats[145,149] and in rabbits.[55,142] The less acute myocardial lesions seen in older infants bear a resemblance to the later lesions reported in rats.[149] The myocardial fibrosis and atrophy seen in the children or young adults coming to autopsy with the supravalvular aortic stenosis syndrome may possibly represent the final cardiac phase of the disease. It is not known whether overdosage with vitamin D may contribute to renal calcinosis and cardiovascular disease in later life.

The stigmata of the Williams' syndrome include supravalvular aortic stenosis, mental retardation and a characteristic facies. Children with this disease resemble survivors of hypercalcemia of infancy, a disease associated with hyper-reactivity to vitamin D. The pathologic lesions of infants with acute hypercalcemia seen at autopsy[23,52,62,66,96,98] resemble those seen during the acute or subacute phase of experimental hypervitaminosis D in the laboratory,[141-154] and those reported in infants with generalized arteriosclerosis.[131,132,155-160] Arterial changes include intimal and/or subintimal thickening, with fragmentation and degeneration of the internal elastic lamina, and medial degenerative changes, thickening, and metastatic calcification, particularly in the aorta. In the kidneys are seen glomerular ischemia, with endothelial proliferation, periglomerular fibrosis, reduction in numbers of tubules, flattened tubular epithelium, hyaline, granular, or calcareous casts, and calcium deposits in lining cells and in basement membranes. Survivors of the acute phase of the disease, who had the peculiar facies characteristic of the Williams' syndrome, and who exhibited cardiac damage, hypertension, and supravalvular stenosis, at autopsy[7,24,34,78] were found to have had lesions that resembled the supravalvular aortic lesions reported by Perou in "congenital" aortic stenosis,[5] and by Gillman and Gilbert[149] late in the course of vitamin D toxicity in rats. It is noteworthy that the aortic stenotic lesions described by Friedman and Roberts[156] in three-month-old rabbits, whose mothers had been given an enormous dose of vitamin D during gestation, were similar both to those reported by Perou[5] and by others[9,11,33] in clinical supravalvular stenosis and to the lesions in rats after loading with vitamin D.[149] The renal changes seen in such children either at autopsy or after biopsy included contracted, granular kidneys with numerous areas of calcification[7,24,33,74,101] and were similar to those seen as a late expression of vitamin D toxicity in the experimental animal.[141,144]

From the available evidence, it seems unlikely that the pathologic findings in these severe clinical syndromes, which are so similar to those produced experimentally by toxic doses of vitamin D, can be merely coincidental. Great variations in the responses to vitamin D in animals and in man have been recognized. It has long been accepted that Negro infants are unduly susceptible to rickets, and because of relative resistance to the anti-rachitic activity of vitamin D, often require higher prophylactic doses of vitamin D than do white infants, as well as much higher therapeutic doses. That at the other end of the spectrum are children (predominantly white) who need very little vitamin D, who are very susceptible to this vitamin, and who cannot tolerate even slightly elevated doses over minimal amounts, has not been realized. From the data reported in 1937 by Drake,[123] it appears that a significant number of children

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of British or Northern European origin require little or no more vitamin D than is obtained from nonfortified foods and from sunshine. Confirmation of the lesser daily vitamin D requirements of white children, as compared with those of Negroes, was reported by Lewis.[124] He found that none of the white children observed over a five-month (winter) period of no vitamin D supplementation developed rickets, whereas 62% of the Negro children without vitamin D during the same time did. The significance of the ability of some children to remain free of rickets in the absence of outside sources of vitamin D has not been analyzed. One may speculate that it may be the result of a genetic mutation, which allowed for thriving of children who live in areas where exposure to sunlight is uncertain and where other sources of vitamin D are unreliable. With the coming of the public health era, with its emphasis on supplying all infants with such supplemental amounts of vitamin D as have been found necessary for those most susceptible to rickets, this presumed metabolic advantage may have become a liability. It must be noted that this genetic variant is apparently not limited only to the white race, despite the far greater frequency of the disease resembling hypervitaminosis D in fair-skinned children. Two Negro infants with generalized arterial calcification,[98,136] which may be the most extreme expression of high susceptibility to vitamin D, and several Negro children with supravalvular aortic stenosis have been reported.[10,33] On the basis of the available evidence, it seems likely that the genetic variant that results in poor responsiveness to vitamin D, thereby protecting against vitamin D toxicity, but increasing susceptibility to rickets, is more common in Negroes. On the other hand, the variant associated with markedly high responsiveness to vitamin D that protects against rickets and that increases susceptibility to vitamin D toxicity seems to be more common in fair-skinned children.

The amount of vitamin D recommended as a daily supplement was selected on the basis that it should be sufficient to protect against rickets in at least 98% of the total population. The data used were probably obtained from Lewis's[124] study, which showed that even at 1,450 units/day, one Negro child still developed rickets. On that account, he recommended addition of 332 units of vitamin D to milk to achieve at least the protective value of 1,450 units in oil. That 332 units in milk may exert an even greater anti-rachitic effect than 1,450 units in oil is suggested by Lewis' work[130] indicating that 90 units of vitamin D in milk was therapeutically more effective than 900 units in oil. In fact, he found 45 units in milk to be curative in six of eight rachitic infants; the remaining two, who required higher doses, were Negroes.

Warkany and Mabon's[133] demonstration of significantly higher blood levels of vitamin D in white than in Negro children was the first bit of direct laboratory evidence that there are wide variations in serum anti-rachitic values. Fanconi and Schwartz,[91] who reported exceedingly high levels of anti-rachitic activity in the blood of hypercalcemic children, even when given no exogenous vitamin D and when protected from sunlight, provided the second clue to the pathogenic role of high serum anti-rachitic values. Forfar's[65,77,150] observation that cholesterol levels are markedly elevated in hypercalcemic infants, and that some cholesterol derivatives have vitamin D-like activity, is an important piece of evidence that anti-rachitic factors in the serum are responsible for the disease, hypercalcemia of infancy. He has postulated that susceptible infants have vitamin D percursors that are activated by synthetic vitamin D.[120] This may prove to be true. Another possibility that available evidence suggests is that the addition of crystalline vitamin D to milk, by enhancing its potency three-to tenfold, may be causing vitamin D toxicity directly in such children, whose

vitamin D requirements are very low.

The possibility that the syndrome of infantile hypercalcemia may be caused by overdosage with vitamin D during pregnancy has been suggested.[8,99,154] That vitamin D overdosage, especially to pregnant women who may be unduly susceptible to vitamin D, may cause fetal damage seems probable. Thus far, however, search through the literature for verified instances of overdosage with vitamin D during pregnancy of mothers of infants with the syndromes described in this paper has failed to reveal any such cases. In fact, a normal infant was born to a mother who had accidently taken high daily doses of vitamin D for two weeks early in her gestation period.[155] Since she had an older child with the Williams syndrome, the failure of the vitamin load to cause infantile hypercalcemia is quite significant. Earlier reports of questioning of mothers of children with infantile hypercalcemia revealed that in the ten from whom data were obtained, there were intakes no higher than 1,000 units daily during their pregnancy.[7,25,26,46,103,156] In generalized arteriosclerosis of infancy, resulting in death by two months of age, which would appear to be more likely to have been caused by prenatal insult, evidence that vitamin D had not been taken during pregnancy was given in two instances.[122,158] Since infants are known to have immature enzyme systems, it seems more likely that administration of vitamin D during early infancy to hyper-reactive infants is the cause of these pediatric diseases than is its administration during pregnancy.

These observations raise the question: Just what are the best means of assuring optimum protection against rickets in children with high vitamin D requirements, without at the same time precipitating cardiovascular, renal, and possibly mental, disease in children with very much lower requirements, who may be hyper-susceptible to vitamin D? In the case of a substance to which there is such a wide variation in response, the amount unavoidably taken by those on a recommended diet should not exceed that found to be anti-rachitic in the group most susceptible to the action of vitamin D. The larger requirements of children more susceptible to rickets should be provided by specific supplements. Whether there should be addition of vitamin D to foods, including milk, should be reconsidered. The demonstrated increased potency of vitamin D in milk and the variability in the amount ingested make it difficult to guard against ingestion of doses that are potentially harmful.

## SUMMARY

1. The striking histopathological similarity of several serious diseases of infancy and childhood that are characterized by cardiovascular, renal, and brain damage, to the changes seen in experimental vitamin D toxicity, points to vitamin D as an important etiological factor in these diseases.

2. There is strong evidence that hypercalcemia of infancy is caused by hyper-reactivity to vitamin D, as indicated by (a) the increased incidence of the disease in England during a period of overdosage with vitamin D; (b) its occurrence in infants given massive doses of vitamin D; (c) demonstration of increased anti-rachitic activity of the blood of affected infants; and (d) metabolic evidence of increased response to vitamin D by such infants.

3. Supravalvular aortic stenosis, mental retardation, and characteristic facies constitute a syndrome that is strikingly similar to that seen in survivors of hypercalcemia of infancy, and to that which has been reported in children given massive doses of vitamin D during infancy and early childhood.



4. Evidence is presented that renal tubular acidosis and nephrocalcinosis infantum may be less severe manifestations of hyper-susceptibility to vitamin D, and that generalized infantile arteriosclerosis may be a more severe manifestation.

5. The racial difference in susceptibility to vitamin D may account not only for the higher susceptibility of Negro infants to contract rickets, but also for the apparently greater susceptibility of fair-skinned children to develop conditions such as infantile renal acidosis, hypercalcemia, generalized arterial calcification in infancy, and the supravalvular aortic stenosis syndrome.

6. The enhanced activity of vitamin D in milk, three-to tenfold, as compared to the same unitage in oil, delivers excessive quantities of vitamin D to those drinking milk freely. Four hundred units in oil have been shown to be prophylactic even in the group most susceptible to rickets, and to exceed considerably that required by those least susceptible to rickets.

7. The question of the amount of vitamin D to be used as a prophylactic supplement should be re-investigated. The daily prophylactic dose should not exceed that shown to be safe for children most reactive to vitamin D. Larger amounts should be prescribed for those more susceptible to rickets.

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**UNITED STATES COURT OF APPEALS**
**SECOND CIRCUIT**
**STATE OF NEW YORK**

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**THE NATIONAL NUTRITIONAL FOODS ASSOC. and SOLGAR, CO., INC.,**

**Plaintiffs-Appellants,**

*against*

**F. DAVID MATHEWS, et al.,**

**Defendants-Appellees.**

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*Index No.*

*Affidavit of Personal Service*

*STATE OF NEW YORK, COUNTY OF* NEW YORK *ss.:*

*I,* **James A. Steele** *being duly sworn, depose and say that deponent is not a party to the action, is over 18 years of age and resides at* 310 West 146th Street, New York, New York

*That on the* **10th** *day of* **November** *19* **76** *at* **1 St. Andrews Plaza New York, N.Y.**

*deponent served the annexed* exhibit (vol. 182) *upon*

**Robert B. Fiske, Jr. Attn.: Asst. U.S. Attorney Naomi Reece Buchwald**

*the* **attorney** *in this action by delivering a true copy thereof to said individual personally. Deponent knew the person so served to be the person mentioned and described in said papers as the herein.*

*Sworn to before me, this* **10th** *day of* **November** *19* **76**

Beth A. Hirsh
BETH A. HIRSH
NOTARY PUBLIC, State of New York
No. 41-4623156
Qualified in Queens County
Commission Expires March 30, 1978

James A. Steele
JAMES A. STEELE